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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001482
Article Type:	Research
Date Submitted by the Author:	13-Aug-2012
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	General practice / Family practice, Infectious diseases, Epidemiology, Emergency medicine, Ear, nose and throat/otolaryngology
Keywords:	Paediatric A&E and ambulatory care < PAEDIATRICS, Paediatric infectious disease & immunisation < PAEDIATRICS, Epidemiology < INFECTIOUS DISEASES, Paediatric otolaryngology < OTOLARYNGOLOGY

Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables

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Funding: none

Conflict of interest: none

ARTICLE SUMMARY

Article focus

- Pharyngitis is a frequent diagnosis in children leading to excessive antibiotic treatments by the inability to distinguish a bacterial and viral cause of the disease despite the availability of rapid diagnostic test, too rarely done in children with pharyngitis.
- Several studies avec analyzed the performance of clinical signs and developed clinical decision rules for the diagnosis of group A streptococcal (GAS) pharyngitis in children.
- Through a meta-analysis, this article focus on the methodological quality of these studies and on the value of clinical signs and decision rules that could be helpful to focus rapid diagnostic test to the children with higher risk of GAS pharyngitis.

Key messages

- No symptom considered alone is predictive enough of GAS pharyngitis.
- Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children.
- Clinical decision rules could help clinicians to focus rapid diagnostic tests to children with high risk of GAS pharyngitis to reduce the use of antibiotic.

Strength and limitations

- Meta-analysis of all relevant articles, from 1975 to 2010 that analyzed the performance of clinical signs and derived or validated clinical decision rules for the diagnosis if GAS pharyngitis in children.
- A decision rule that performed as well as most rapid diagnostic tests was identified, but has not been validated until now.
- Comparison between studies was limited by methodological weaknesses and heterogeneity between patients.

ABSTRACT

Objective: To identify the best clinical decision rules (CDRs) for diagnosing group A streptococcal (GAS) pharyngitis in children. A combination of symptoms could enable clinicians to predict which cases of pharyngitis in children might be GAS infections.

Design: Systematic review and meta-analysis of original articles, which derived or validated a CDR in children. The Pubmed, OVID, INIST and Cochrane databases from 1975 through 2010. The databases were screened for articles that derived or validated a CDR on a pediatric population: 171 references were identified.

Setting: Any reference including primary care for children with pharyngitis.

Data extraction: The methodological quality of the articles selected was analyzed according to published quality standards. A meta-analysis was performed to assess the statistical performance of the CDRs and their variables for the diagnosis of GAS pharyngitis.

Primary outcome measure: The main criterion was a false-negative rate in the whole population not any worse than that of a rapid diagnostic test strategy for all patients (high sensitivity, low negative likelihood ratio).

Results Four derived and 12 validated CDRs for this diagnosis in children. These articles involved 10,523 children (mean age, 7 years; mean prevalence of GAS pharyngitis, 34%). No single variable was sufficient for diagnosis. Among the CDRs, that of Joachim et al. had a negative likelihood ratio of 0.3 (95%CI: 0.2-0.5), resulting in a post-test probability of 13%, which leads to 3.6% false-negative rate among low-risk patients and 10.8% overall, equivalent to that of some rapid diagnostic tests.

Conclusion The rule of Joachim et al. could be useful for clinicians who are reluctant to use rapid diagnostic tests and should allow them avoid antibiotic treatment for children who do not have GAS pharyngitis. It could thus lead to a more rational use of rapid diagnostic tests for those children at higher risk of GAS pharyngitis.

Trial registration: no

Introduction

Acute pharyngitis is one of the most common diseases in the world. It is diagnosed annually in 11 million patients in US emergency departments (ED) and other outpatient settings [1] and is responsible for more than 140 physician office visits and 96 antibiotic prescriptions per 1000 US children under 15 years of age [2]. The group A streptococcal (GAS) form is identified in 20 to 37% of children with pharyngitis [3,4].

The priority over the past 50 years has been the prevention of GAS complications such as local suppurations, invasive infections, and acute rheumatic fever (ARF). These complications are rare in industrialized countries, however; among children treated with antibiotics in GAS pharyngitis, less than 1% have suppurative complications [5], 3/100,000 have invasive infections [6] and 0.08 to 0.15/100,000 ARF [7,8]. ARF rates were declining even before the use of antibiotics because non-rheumatogenic types of streptococci were replacing the rheumatogenic types [9]. The prevention of these complications, however, has induced the large-scale prescription of antibiotics, which in turn might induce drug side-effects and the emergence of multidrug-resistant organisms due to pressure on the ecosystem [10].

National guidelines are different one country to another [11]. To optimize the use of antibiotics, in 2002 the Infectious Diseases Society of America (IDSA) recommended the use of pharyngeal swabs to take samples for bacterial cultures or rapid diagnostic tests (RDT) when physicians cannot clinically rule out a bacterial cause of the pharyngitis [12]. These recommendations have changed some medical practices, but adhesion remains partial [13]. Although diagnostic performances of RDT are good (sensitivity [Se], 85-90%, specificity [Sp], 90-100%) [14,15], they are still not widespread used [16], are offered to less than 50% of patients with pharyngitis [17], and antibiotic prescriptions for children with pharyngitis remain excessive in industrialized countries [2]. Clinical decision rules (CDRs) have been

proposed to help physicians decide whether or not the patient needs further tests (RDT or culture) or direct antibiotic treatment without further testing. The IDSA recommends the use of such CDRs [12]. Although several authors have suggested CDRs for children [18-23], most of these have been validated only partially [24-35].

The aim of this study is to conduct the first systematic review, including a meta-analysis, of these CDRs and their variables for the diagnosis of GAS pharyngitis in children, to identify CDRs not any worse than that of a rapid diagnostic test strategy.

Methods

Search strategy and study selection criteria

To identify eligible original articles, we searched four electronic databases: Medline via PubMed, INIST (Institute for Scientific and Technical Information) at article@inist, the OVID library at www.ovid.com, and the Cochrane library. In the Medline search, we used the medical subject heading (MeSH) terms "pharyngitis" (restricted to major topic) and "predictive value of tests", separated by the Boolean operator AND. Limits were set to specify "human" as the species, "all child" as the age, and year of publication from 1975 to 2010, without limits on language of publication. In INIST, we used the terms "pharyngitis" and "children". In OVID, we used the terms "pharyngitis", "children" and "sensitivity". In the Cochrane library, we used the term "pharyngitis" alone to broaden the research.

The study selection criterion was the presence of original data used to derive or validate a CDR for predicting GAS pharyngitis in a pediatric population. We reviewed the titles of all articles identified by electronic searches and then the abstracts of those that appeared eligible. Related articles and references in the articles that met the selection criterion

were examined to identify references that our electronic research might have missed. Eligible articles were fully reviewed.

Quality criteria for the CDR derivation and validation studies

The quality of the selected articles was determined by applying the methodological standards of Wasson et al. [36] and Laupacis et al. [37]. Two of the authors (FL, FD) separately screened each article for the 10 criteria listed below. Each criterion applied to GAS pharyngitis was split into 1 to 4 items (one point per item), as detailed below. Derivation studies could have up to 24 items and validation studies 21. The criteria were:

(i) The outcome for the selected articles was GAS pharyngitis. It should have been defined and diagnosed with the gold standard, a throat culture. The culture technique should have been specified. The test used as the gold standard should have been assessed blinded, without knowledge of the value of the predictive variables. (ii) The predictive values used in the studies that derived each CDR should have been exhaustively identified and well defined, to facilitate its reproducible use. The choice of the variables should have been explained, and the potentially important variables not included should have been mentioned. The studies that validated CDRs should have used the predictive variables as listed and defined in the derivation. Analysis should have been performed blinded to the outcome. (iii) Important patient characteristics should have been described, e.g., age, sex ratio and any characteristics that might cause the predictive value to differ within the cohort of patients, such as the prevalence of GAS pharyngitis. (iv) The study site should have been specified, including the medical setting and the country. (v) The statistics used to derive the CDRs should have been described and justified. The authors should have assessed the possibility that the logistic regression model overfitted the data [37]. (vi) The statistical performance of the CDRs should have been described. (vii) The reproducibility of the predictive variables and of the CDR

should have been assessed. (viii) The study should have been prospective, and the CDR should have been fully validated, in accordance with recommendations [38]: derivation study, internal validation, external validation, and prospective study of the rule's impact on clinical behavior. (ix) The CDR should be clinically sensible, easy to use (simple and quick) and should suggest a course of action rather than a probability of disease. (x) The effects of clinical use should have been prospectively measured. This last criterion (impact of the CDR) was evaluated at point viii.

Main criteria of CDR performance

The aim of a CDR strategy is to identify a group of children at low risk of GAS pharyngitis to allow them to avoid antibiotic treatment for these patients and to propose an action (e.g., RDT) for patients classified in the high-risk group. A strategy including a CDR was considered useful if it did not increase the false negative rate in the overall population (high and low risk patients), compared to a RDT strategy for all patients (Figure 1). The RDT strategy (median Se: 89%, median Sp: 96%) has a median false negative rate of 11% [14]. Therefore, our criteria for evaluating the performance of each CDR were a Se as good as that of RDTs and a probability of GAS pharyngitis in the low-risk group of patients <11%. This corresponds to a negative likelihood ratio (LR–) of 0.2 or less when the prevalence of GAS pharyngitis is 30% [3, 4]. In the literature, a LR– under 0.2 is considered useful [37] and the median LR– for RDTs is 0.15 [14].

Statistical analysis

After the identification of the CDRs, the entire population was described, in percentages and 95% confidence intervals (CI) for dichotomous variables and means and ranges for

continuous variables. The absence of the raw data prevented us from calculating the standard deviations. The statistical performance of the variables and the CDRs was analyzed for pediatric studies only and not in studies that included both children and adults. When possible, we focused on children older than 3 years [26], because younger children rarely have GAS pharyngitis [12].

The meta-analysis of the variables included in the CDRs and their validations used the DerSimonian and Laird method [40]. For the Se, Sp, positive and negative predictive values (PPV and NPV), we tested the heterogeneity between studies, applying the likelihood ratio test. For the odds ratio (OR), positive likelihood ratio (LR+) and LR–, we used Cochran's Q test. In analyses with significant heterogeneity or with four or more studies, a random effect model was used to assign the weight of each study. Pooled Se, Sp, PPV, NPV, LR+, LR– and OR with their 95% CIs were calculated for CDRs and their variables.

CDRs in the literature propose different courses of action according to the individual's clinical risk of GAS pharyngitis. In the selected studies, four CDRs proposed a course of action based on three levels of probability of GAS pharyngitis: high risk (antibiotics), intermediate risk (culture and antibiotics if positive), and low risk (no culture, no antibiotics). One CDR proposed a course of action based on two risk groups [19], and two CDRs offered four or five risk groups without any courses of action [18,24]. We chose to identify the CDRs with a useful LR– that would allow us to rule out GAS pharyngitis, as most second-generation RDTs do. Therefore we dichotomized each population into two groups: the low-risk group on one side and the intermediate and high-risk group on the other side (see supplementary material).

Results

Search strategy results

Our search strategy identified 65 references from PubMed, another 89 from INIST, 8 from OVID and 9 from the Cochrane database. Reading the titles and abstracts of these 171 references led us to exclude 150 articles that did not meet the inclusion criterion. Complete reading of the remaining 21 articles and reviewing their references, related articles and authors' publications identified 15 additional relevant references. Of these 36 references, 18 were excluded because they did not report the derivation or validation of a CDR on a pediatric population. In the 18 articles that fulfilled the inclusion criterion, six studies derived CDRs [18-23], and 12 validated them in children [24-35]. Of these 18 studies, the article cited as the source from which the World Health Organization's (WHO) CDR [19] was derived did not provide details about it, and the CDR by Centor et al. [18] used for validation in children was derived on adult patients. These two derivation studies were thus screened for methodological quality, but were excluded from the meta-analysis. However, the studies that validated these two CDRs among children [27-30] were included in the meta-analysis.

Patient characteristics

The 16 studies with data for children included 10,523 children. Eleven studies took place in industrialized countries and five in emerging countries. Nine studies were conducted in hospitals or clinics, six in pediatricians' or general practitioners' (GPs) offices, and one in GPs' offices and an ED. Overall, the derivation studies that could be reviewed (n=4) included 963 children (mean number per study: 241, range: 90–356) [20-23]. All the validation studies (n=12) together included 9,560 children (mean number per study: 797, range: 79–1,848) [24-35]. The mean prevalence of GAS pharyngitis was 34% (median: 34%, range: 24–58%) and did not differ between the derivation and validation studies (33% vs. 34%; p=0.54) or

between industrialized and emerging countries (34% vs. 33%; p=0.30). The children's mean age was 7 years, 5.9 in the derivation and 7.2 in the validation sets, 5.7 in the emerging and 8.4 in the industrialized countries. The studies used different inclusion criteria: “pharyngitis” (n=5) [22,23,26,34,35], “suspected GAS pharyngitis” (n=4) [21,25,28,33], “sore throat” (n=3) [27,30,32], “new upper respiratory tract infection” (n=2) [20,24] and both “new upper respiratory tract infection” and “sore throat” (n=2) [29,31].

Methodological quality for derivation and validation studies

Overall, the derivation studies correctly followed a median of 65% of the quality criteria (range: 13-83%). The derivation of WHO’s CDR was not found. The validation studies correctly followed a mean of 69% of these quality criteria (range: 43-86%) (Table 1).

One study used an RDT as the gold standard [23], and two others used RDTs or throat culture [28,33]. No derivation studies defined a predictive variable; three validation studies did so for at least one variable (i.e., cervical lymph node [24,26,29], abnormal pharynx [24], exudate [29]), but 7/12 validation studies changed a variable (e.g., tender node for node, fever≥38°C for fever>38°C). All studies described the CDRs, although one modified it [35]. No study specifically described whether assessments were blinded, but for validation studies, we considered that a prospective study based on the culture result and without any RDT validated this item. One derivation study simplified a rule without reconducting the statistical analyses [23]. Only one study was retrospective [33].

Performance of the variables

The CDRs considered 17 variables in all, most frequently lymph nodes, exudate, age, fever and cough. The supplementary materials include a table describing the types of variables by CDR and the details of the CDRs. Table 2 presents the meta-analysis of the statistical

performance of these variables. “Node >1.5 cm”, “sore throat” and “no diarrhea” each had a LR– under 0.5. The sensitivity of these three variables exceeded 0.81, and their NPV exceeded 0.72. The statistical performance of “Node >1.5 cm” was not reproducible with the other “node” variables. “Scarlatiniform rash” had the highest LR+ (4.7) and OR (4.8). All other LR+ were less than 2.

Performance of the CDRs

After meta-analysis of the validation studies, three rules had high Se (99%, 95% and 88%) and NPVs (87 to 88%). However, the rules of McIsaac et al. and Attia et al. were not discriminative (Sp, 14% and 4%), and were negative for only 10% and 3% of the population respectively (Table 3). These rules were therefore not useful in clinical practice. The rule tested by Joachim et al. had one of the best LR– (Table 3), with a value of 0.3 (95% CI: 0.2-0.5), which should help clinicians to rule out the diagnosis of GAS pharyngitis. Application of this CDR brought the probability of GAS pharyngitis down from 34% to 13% when the score of the CDR is negative (Figure 2). The rule of Joachim et al. also had the best performance, with a Se of 88%, a post-test probability of 13% in 28% of the low-risk patients, and a Sp of 35% (95% CI: 30-40). This rule leads to a 3.6% false-negative rate in this low-risk population and 11.5% overall with an RDT strategy for the intermediate and high-risk patient groups and on the assumption that the RDT sensitivity was 89%.

Discussion

The large number of studies and CDRs proposed for the diagnosis of GAS pharyngitis is evidence of physicians' desire to improve their management of this common disease and to limit antibiotic prescriptions, bacterial resistance and costs. Our study shows how difficult it is to develop and validate an effective and useful CDR. We identified 16 articles that

described the derivation or validation of seven CDRs for the diagnosis of GAS pharyngitis in children. The meta-analysis confirmed, as others recently, [41] that symptoms alone were not sufficient to rule out this diagnosis. Examination of the statistical performance of the variables included in the CDRs showed that none had a significant positive (>5) or negative (<0.2) LR [39]. Two CDRs brought the post-test probability of GAS pharyngitis to around 10% [21,23]. Only the CDR of Joachim et al. was considered useful for clinical use to exclude GAS pharyngitis.

The poor performance of each of these variables requires comment. It might be due to the low specificity of some signs (such as rhinorrhea and cervical nodes), their subjectivity in children (sore throat), or a lack of definition. For these reasons, several variables might have been recorded differently from study to study and possibly within some studies. Because the individual variables predict GAS pharyngitis so poorly, researchers have suggested combining potential predictive variables within a CDR. Our systematic review of standards for the derivation of CDRs [36,37], however, shows that none of the studies followed all of the methodological quality criteria, in particular, the studies that derived CDRs did not. The construction of two CDRs was not available for methodological analysis [19,24,42]. A rule that proposed an empirical simplification of the Breese score, without following any methodological standards was not included [43]. Two other rules not specifically derived for children [18,20], have nonetheless been used for validation in a paediatric population [27,28,31-34], despite the methodological requirement that rules be applied only in populations with the same characteristics as those used in the derivation sets [38]. We also identified statistical biases. When a CDR is derived on a population, the validation set should not include members of the derivation set [20]. Moreover, the logistic regression model of multivariate analyses in some studies might have been overfitted [18,22]. Finally, the validation of a CDR may entail its refinement [23,35], which in turn requires a new

validation. The CDRs with the lowest LR– in our meta-analysis were those of Attia et al. [21] and Joachim et al [23], which brought the post-test probability of GAS pharyngitis down to 9 and 13% respectively. Nonetheless, the CDR by Attia et al. was validated only once [35] and was not discriminative for clinical practice. The rule developed by Joachim et al. performed best but has not been externally validated yet and requires the collection of nine variables for its application, which may limit its use in practice. Since CDRs were more useful than individual symptoms, they might help the clinicians who do not use RDTs in ruling out the diagnosis of GAS pharyngitis. The interquartile range of LR– for second-generation RDTs varies from 0.07 to 0.19 [14]. Thus the probability of GAS pharyngitis would have been reduced from 34% to a post-test probability of less than 10% for most RDTs [14,15]. Compared to this full RDT strategy, the CDR of Joachim et al. leads to a maximum 11.5% false-negative rate globally: 3.6% in the low-risk group of patients (28%) and 7.9% in the intermediate and high risk group (72%), if we assume a RDT strategy with 89% sensitivity (probably an underestimate in this group). Nevertheless, none of the CDRs included in this study reached the level of performance required to bring both the probability of GAS pharyngitis and the risk of a false negative test to less than 10%, as most RDTs do.

Our study has some limitations. Because of the lack of access to individual data, except from two authors who provided the complete set of data from their derivation study [22,23], we could only perform a meta-analysis of the pooled data. Moreover, the populations involved in our analysis were heterogeneous and difficult to compare. These differences concerned (i) the objective of the study, since some studies sought to validate a CDR while others tested RDTs [34] or serologic titers [27]; (ii) the inclusion criteria, which differed between CDRs and even within the same CDR; and (iii) the mean age of the patients, which might influence the prevalence of the disease and the type of symptoms [26]. The prevalence of the disease varied and could double between studies, as a result of differences in patients'

ages [30] or study sites or because of a short study period when GAS might be more or less prevalent [18,21,24]. Although prevalence did not influence sensitivity, specificity or the LRs of the variables, it might influence the choice of variables for building the CDR, especially when methodological standards are not adhered to closely. A spectrum bias is possible if reference standards were not performed in all patients of the included studies. Variables might be defined differently between studies of the same CDR, and one CDR might suggest a different course of action in different studies [35]. Another important variation may come from the definition of the disease (pharyngitis), which was not provided in the studies and which varies between countries [12,44]. We had to create artificial risk groups and courses of action for three CDRs, although they had not been derived for that purpose; our results thus cannot reflect exactly the performance of each risk group. Finally, a review was recently published on this subject but focused the literature research on the signs and symptoms of pharyngitis, when we focused it on CDRs. Findings were slightly different in terms of articles reviewed and not different in terms of performance of individual variables. The CDR by Attia et al. was identified by their systematic research but not the one by Joachim et al [41].

Lastly, we must question whether physicians will use a CDR at all for a well-known and usually banal disease. It might well interest the 50% of physicians who do not use RDTs at all [13,16,17]. It will do so only, however, if the CDR produces accurate results, is useful, is well validated and is easy to use. The heterogeneity of patients between studies might necessitate a validation and a comparison of available CDRs in a single pediatric population. Our results showed that one CDR has a performance that did not produce a false-negative rate for GAS pharyngitis higher than that of the RDT strategy [19]. However an external validation in different resource settings may be warranted before generalization. After validation, this CDR might help physicians to focus RDTs on children at higher risk of GAS pharyngitis and therefore decrease antibiotic prescriptions for children in the low-risk group.

Contributors

Study concept and design; study supervision: FLM, FD, IP, AM.

Acquisition of data: FLM.

Analysis and interpretation of data; critical revision of the manuscript for important intellectual content: FLM, FD, AD, IP, AM.

Drafting of the manuscript: FLM, FD, AM.

Statistical analysis: FLM, FD, AD.

Le Marechal and Dubos (guarantor) have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosures none

Funding none

Competing interest none

Ethics approval No ethical approval was needed for this pooled data meta-analysis

Data sharing statement There is no additionnal data available

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Fig 1. Expected performance of a clinical decision rules strategy for group A streptococcal pharyngitis in children compared to the rapid diagnostic test strategy.

Fig 2. Post-test probability of the clinical decision rules (CDRs) for the low-risk group of patients compared with the performance of the rapid diagnostic tests on Fagan's nomogram. The pre-test probability considered (prevalence of the disease) was 34%.

Table 1. Methodological Quality of the Selected Studies that Derived or Validated Clinical Decision Rules for the Diagnosis of Group A Streptococcal Pharyngitis in Children

Quality criteria [35,36]	Breese [23]	Funamura [24]	Karacan * [25]	Centor † [17]	Dagnelie [26]	Hall [27]	WHO † [18]	Steinhoff [28]	Rimoin [29]	McIsaac † [19]	McIsaac [30]	McIsaac [31]	Edmonson [32]	Tanz [33]	Attia † [20]	Attia [34]	Smeesters † [21]	Joachim † [22]
Children	670	892	857	0	79	561	MD	451	1810	90	167	454	1184	1848	297	587	220	356
/total population	/670	/892	/857	/234	/558	/561		/451	/1810	/521	/620	/787	/1184	/1848	/297	/587	/220	/356
Outcome																		
GAS pharyngitis	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
Culture	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	0
Culture described	0	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1
Blind assessment	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Variables																		
Defined	NC	NC	NC	0	NC	NC	0	NC	NC	0	NC	NC	NC	NC	0	NC	0	0
Choice explained	NC	NC	NC	0	NC	NC	0	NC	NC	0	NC	NC	NC	NC	0	NC	1	1
Important variables	NC	NC	NC	1	NC	NC	0	NC	NC	1	NC	NC	NC	NC	1	NC	0	0
Same variables	0	0	0	NC	0	0	NC	0	1	NC	0	1	1	1	NC	0	NC	NC
Blind assessment	1	1	1	0	0	0		1	1	0	1	0	1	0	0	1	0	0
Patients' characteristics																		
Age (years)	MD	0-16	MD	>15	4-14	2-17	MD	2-13	2-12	3-14	3-14	3-17	MD	3-18	0.5-18	MD	0-15	0-15
Mean/median age	MD	MD	5.6	MD	‖	9	MD	MD	5.1	‖	MD	‖	8.4¶	9.3	6.2	6.8	6.6	5.4
Sex ratio	MD	MD	1.2	MD	MD	0.9	MD	1.1	1.3	‖	‖	MD	0.9	0.9	1.1	1.0	1.3	1.1
Prevalence GAS (%)	54	28	49	‖	58	27	MD	24	29	36	35	34	32	30	29	37	26	33

Table 1 continued

Study site																		
Medical setting	GP	clinic	hospital	ED	GP	ED, GP	MD	hospital	clinic	GP	GP	GP	clinic	GP	ED	ED	ED	ED
Country	US	US	TUR	US	NL**	US	MD	EG	BR,EG,HR	CA	CA	CA	US	US	US**	US**	BR	BR
Statistics																		
Described	NC	NC	NC	1	NC	NC	0	NC	NC	1	NC	NC	NC	NC	1	NC	1	1
Logistic regression	NC	NC	NC	1	NC	NC	0	NC	NC	1	NC	NC	NC	NC	1	NC	1	0
Outcome/variable	NC	NC	NC	0	NC	NC	0	NC	NC	1	NC	NC	NC	NC	1	NC	0	0
Performance described	0	1	1	0	1	1	0	1	1	1	1	1	1	1	0	1	1	1
CDR Reproducibility	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Development ††	3	3	3	1	3	3	0	3	3	2	3	3	0	3	1	3	2	2
CDR practical use																		
Clinically sensible	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Easy to use	0	0	0	1	1	1	1.	1	1	1	1	1	1	1	1	1	0	0
Course of action	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Total score:	9‡‡	12‡‡	13‡‡	14†	13‡‡	14‡‡	3†	16‡‡	18‡‡	20†	15‡‡	16‡‡	13‡‡	17‡‡	16†	16‡‡	17†	15†
N/24† or N/21‡‡ (%)	(43)	(57)	(62)	(58)	(62)	(67)	(13)	(76)	(86)	(83)	(71)	(76)	(62)	(81)	(67)	(76)	(71)	(63)

*children>3 years old only; † derivation studies; ||validated, but adult and pediatric data; ¶estimated with the number of children per age group; **not provided in the articles; †† development of the rule [37]: derivation study (1 point), internal validation (2 points), external and prospective validation (3 points) and impact of the rule on clinical behaviour (4 points); ‡‡: validation study. 1: validated; 0: not validated, although not specified; BR: Brazil; Ca: Canada; ED: emergency department; EG: Egypt; GAS: group A streptococcal; GP: general practitioner; HR: Croatia; MD: Missing data; NC: Not concerned; NL: Netherlands; TUR: Turkey; US: United States of America; WHO: World Health Organization.
Each study present criterion for patient characteristics and medical setting worth one point each.

Table 2. Meta-analysis of the Statistical Performance of the Predictive Variables for the Diagnosis of Group A Streptococcal Pharyngitis in Children

Variables	References	Pop (n)	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR– (95% CI)	OR (95%CI)
Positive symptoms									
Tender cervical node									
Node : any size	[20-22,27,28,32]	3067	45 (42-48)	71 (69-73)	40 (37-43)	76 (74-77)	1.6 (1.5-1.8)	0.7 (0.7-0.8)	2.3 (1.9-2.8)
Node > 1.5 cm	[28]	451	81 (73-88)	45 (40-50)	32 (26-37)	89 (83-92)	1.5 (1.3-1.7)	0.4 (0.3-0.6)	3.6 (2.1-6.1)
Node > 2 cm	[25]	857	40 (36-45)	78 (74-81)	63 (57-69)	58 (54-62)	1.8 (1.3-2.5)	0.8 (0.7-0.9)	2.4 (1.8-3.2)
Pharynx									
Abnormal pharynx	[25]	857	42 (37-46)	77 (72-80)	63 (57-68)	58 (54-62)	1.8 (1.3-2.5)	0.8 (0.6-0.9)	2.3 (1.7-3.1)
Pharyngeal exudate	[20,27,28]	1308	31 (26-36)	81 (78-83)	37 (32-42)	77 (74-79)	1.6 (1.3-1.9)	0.9 (0.8-0.9)	2.0 (1.5-2.6)
Swollen tonsils	[20,32]	1481	58 (54-63)	57 (54-60)	39 (35-42)	75 (72-78)	1.3 (1.2-1.5)	0.7 (0.7-0.8)	1.9 (1.5-2.3)
Fever									
History of fever (HF)	[27,28]	1006	70 (65-75)	32 (29-35)	26 (23-30)	76 (71-80)	1.1 (1.0-1.1)	0.9 (0.7-1.1)	1.2 (0.9-1.7)
Fever > 38°C	[20,25,28,32]	2789	53 (50-56)	56 (54-59)	40 (37-43)	68 (66-71)	1.1 (1.1-1.5)	0.9 (0.8-1.1)	1.3 (1.1-2.2)
Fever > 38,5°C	[21,22]	576	64 (57-70)	28 (24-33)	28 (24-32)	64 (57-70)	0.9 (0.8-1.0)	1.2 (1.0-1.6)	0.7 (0.5-1.1)
HF or >38°C	[20,25,27,28,32]	3795	56 (54-60)	49 (47-51)	35 (33-37)	70 (67-72)	1.1 (1.1-1.3)	0.9 (0.8-1.1)	1.3 (1.1-1.9)
Headeache	[20-22,25]	1730	51 (48-55)	64 (61-67)	48 (44-51)	67 (64-70)	1.3 (1.1-1.5)	0.9 (0.8-1.0)	1.5 (1.2-2.2)
Sore throat	[25,32]	2041	86 (83-88)	27 (25-30)	43 (41-46)	75 (71-78)	1.2 (1.1-1.2)	0.5 (0.4-0.6)	2.5 (2.0-3.2)
Scarlatiniform rash	[20]	297	14 (8-23)	97 (93-98)	63 (41-81)	74 (68-79)	4.7 (2.1-10.5)	0.9 (0.8-1.0)	4.8 (1.8-12.7)

Table 2 continued

Petechia on the palate	[20-22]	873	20 (16-25)	88 (86-91)	42 (34-51)	72 (69-75)	1.8 (1.3-2.5)	0.9 (0.9-1.0)	2.0 (1.3-2.9)
Sudden onset	[21,22]	576	32 (26-39)	69 (65-74)	31 (25-38)	70 (65-74)	1.1 (0.8-1.4)	1.0 (0.9-1.1)	1.1 (0.7-1.6)
Negative symptoms									
No cough	[21,22,25,27,28,32]	3627	65 (63-68)	55 (53-57)	43 (41-45)	75 (73-77)	1.5 (1.4-1.7)	0.6 (0.6-0.7)	2.4 (2.1-3.1)
No rhinorrhea	[20-22,25,28,32]	3365	71 (69-74)	50 (48-52)	43 (41-45)	76 (74-79)	1.3 (1.3-1.5)	0.6 (0.6-0.8)	2.2 (1.9-3.3)
No abdominal pain	[20-22]	873	69 (64-75)	29 (26-33)	30 (26-33)	69 (64-74)	1.0 (0.9-1.1)	1.1 (0.8-1.3)	1.0 (0.7-1.3)
No diarrhea	[21,22,25]	1433	94 (92-95)	12 (10-14)	43 (40-45)	72 (65-79)	1.1 (1.0-1.1)	0.5 (0.3-0.7)	2.3 (1.5-3.4)
No conjonctivitis	[21,22]	576	100 (NC-100)	6 (4-8)	32 (28-36)	100 (NC-100)	1.0 (1.0-1.0)	NC	NC
No viral exanthema	[21,22]	576	88 (83-92)	2 (1-3)	28 (25-32)	22 (11-38)	1.0 (1.0-1.0)	8.4 (3.2-21.6)	0.1 (0.0-0.3)

Pop: population; n: number of children; Se: sensitivity; CI: confidence interval; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; OR: odds ratio; NC: not calculable

PPV and NPV should be interpreted with the prevalence of the disease in each study, available in Table 1.

Table 3. Meta-analysis of the Statistical Performance of Validation Studies of Clinical Decision Rules for Group A Streptococcal Pharyngitis in Children (Low vs. Intermediate and High Risk)

Initial CDR (First author)	Reference	Children /total	Se (95%CI)	Sp (95%CI)	PPV (95%CI)	NPV (95%CI)	LR+ (95%CI)	LR– (95%CI)	OR (95%CI)	% of patients at low risk
Breese	[23-25]	2419/2419	63 (60-66)	83 (81-85)	74 (71-77)	76 (73-78)	3.2 (2.8-3.6)	0.7 (0.6-0.7)	7.6 (6.2-9.3)	64
Centor	[26,27]	640/1119	41 (34-48)	85 (81-88)	55 (47-62)	76 (72-80)	2.0 (1.6-2.7)	0.8 (0.7-0.8)	3.2 (2.1-4.8)	77
McIsaac	[30,32,33]	3187/3652	95 (94-96)	14 (13-15)	33 (32-35)	87 (83-90)	1.1 (1.0-1.1)	0.4 (0.3-0.5)	3.2 (2.3-4.4)	10
WHO	[28,29]	2261/2261	6 (4-8)	96 (95-97)	37 (28-46)	73 (71-75)	1.6 (1.1-2.4)	1.0 (1.0-1.0)	1.6 (1.1-2.5)	95
Attia	[34]	545/545	99 (97-100)	4 (3-7)	39 (35-44)	88 (66-97)	1.0 (1.0-1.1)	0.2 (0.1-0.9)	4.9 (1.1-21.5)	3
Smeesters	[21]	220/220	84 (73-91)	41 (34-49)	33 (26-41)	88 (79-94)	1.4 (1.2-1.7)	0.4 (0.2-0.7)	3.7 (1.7-8.1)	35
Joachim	[22]	576/576*	88 (82-92)	35 (30-40)	37 (33-42)	87 (81-91)	1.4 (1.2-1.5)	0.3 (0.2-0.5)	4.0 (2.4-6.6)	28

*Results that concerned the population of Smeesters et al. and Joachim et al.'s study
CDR: clinical decision rule; Se: sensitivity; CI: confidence interval; Sp: specificity; PPV: positive predictive value of the test; NPV: negative predictive value of the test;
LR+: positive likelihood ratio; LR–: negative likelihood ratio; OR: Odds ratio; NC: not calculable.
The thresholds for low-risk groups were: Breese: score ≤ 29 (18-29); Centor: score ≤ 2 (0-2); McIsaac: score ≤ 1 (0-1); WHO: absence of ADP and exudate; Attia: 0 symptoms; Smeesters: score ≥ 8; Joachim: score ≤ 2 (0-2)

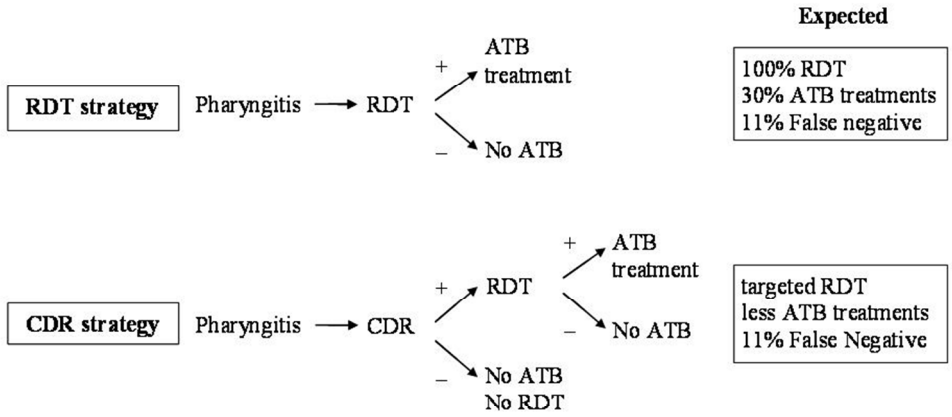

Figure 1.

Figure 1. Expected performance of a clinical decision rules strategy for group A streptococcal pharyngitis in children compared to the rapid diagnostic test strategy

ATB, Antibiotics; CDR, Clinical Decision Rules; RDT, Rapid Diagnostic Test

254x190mm (96 x 96 DPI)

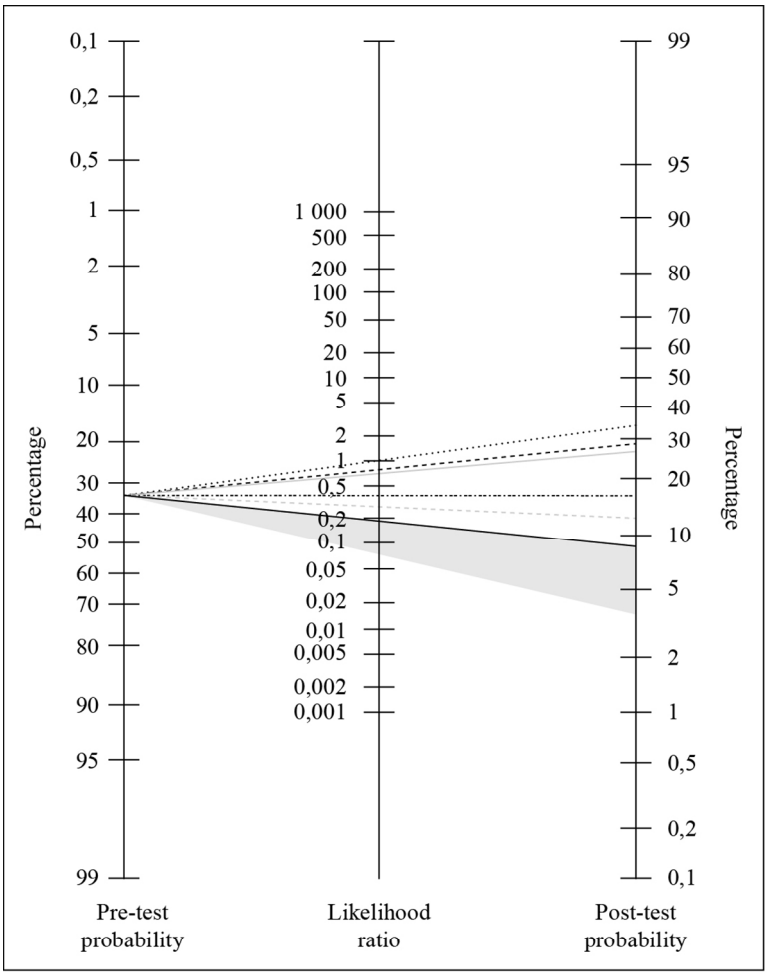

Figure 2. Post-test probability of the clinical decision rules (CDRs) for the low-risk group of patients compared with the performance of the rapid diagnostic tests on Fagan's nomogram. The pre-test probability considered (prevalence of the disease) was 34%.

WHO, World Health Organization

190x288mm (150 x 150 DPI)

Supplementary material

Variables in the Clinical Decision Rules (CDRs) for the Diagnosis of Group A Streptococcal Pharyngitis and Description of these CDRs

Table. Variables of the CDRs Derived for the Diagnosis of Group A Streptococcal Pharyngitis.

Variables	Breese [23]	Centor* [17]	WHO [18]	McIsaac [19]	Attia [20]	Smeesters [21]	Joachim [22]
Cervical lymph nodes	X	X	X	X	X	X	X
Pharyngeal exudate†	X	X	X	X	X		
Age	X			X		X	X
Fever	≥38°C	X#		>38°C		>38.5°C	
Cough	X	X		X		X	
Headache	X					X	X
Sore throat	X						
Sudden onset						X	X
Abdominal pain						X	X
Conjunctivitis						X	X
Diarrhea						X	X
Coryza					X	X	X
Petechia on the palate						X	X
Viral exanthema						X	
Scarlatiniform rash					X		
Month	X						
White blood cell count	X						

*Rule derived in adult patients but validated twice in children
†pharyngeal or tonsillar exudates or swelling
#History of fever

Each CDR is detailed below. The low risk group as determined from identified studies is underlined at the bottom of each CDR.

The CDR derived by Breese et al. [23]

Predictive variable		Points assigned	
Age (years)			
2 or under		1	
3, 15 or more		2	
4, 11 to 14		3	
5 to 10		4	
Months			
July, August, September		1	
June, October, November		2	
January, May, December		3	
February, March, April		4	
Signs and symptoms	**Yes**	**No**	**Unknown**
Fever ≥ 100.5 F	4	2	2
Sore throat	4	2	2
Cough	2	4	4
Headache	4	2	2
Abnormal Pharynx	4	1	3
Abnormal Cervical glands	4	2	3
White blood count			
0-8.4	1		
8.5-10.4	2		
10.5-13.4	3		
13.5-20.4	5		
20.5 or more	6		
Not done	3		

For each patient, they recorded 9 variables, assigned points to each of them, calculated the score and did a throat culture. They created 4 groups: patients with less than 50% risk of GAS pharyngitis were assigned to the groups “no” or “maybe no”; patients with more than 50% were assigned in the groups “yes” or “maybe yes”. A score ≤ 29 defined the low risk group.

The CDR derived by Centor et al. [17]

They derived the CDR on adults. Four of 11 signs and symptoms were statistically correlated with a positive GAS culture: swollen tender anterior cervical node, tonsillar exudates, fever history and lack of cough. Each variable was worth one point. The 5 probability groups had an increasing prevalence of GAS pharyngitis. A score ≤ 2 defined the low risk group.

The CDR derived by the WHO [18]

The WHO recommended in a book that "a child who has tender, enlarged lymph nodes in the front of the neck, and a white exudate on the throat is classified as having streptococcal sore throat". The absence of both clinical signs defined the low risk group.

The CDR derived by McIsaac et al. [19]

The CDR was derived on children and adults. Five of 23 variables were statistically associated with GAS pharyngitis: age, temperature >38°C, no cough, tender anterior cervical adenopathy and swollen tonsils or exudate. Each variable was worth one point. To adjust for age, children aged 3 to 14 years were assigned 1 point, those aged 15 to 44 received a score of 0 and those aged 45 or more received a score of -1. If the total score was :

- 0 or 1: no culture or antibiotic required.
- 2 or 3: culture and antibiotic if positive.
- 4 or 5: culture and antibiotic if positive.

A score ≤ 1 defined the low risk group.

The CDR derived by Attia et al. [20]

Four of the 12 clinical variables screened were statistically associated with GAS pharyngitis: coryza, swollen tonsils, tender enlarged nodes and scarlatiniform rash. Patients were split into 3 probability groups:

- High-risk group: enlarged nodes, swollen tonsils, no coryza with or without scarlatiniform rash (treat, no test).
- Moderate-risk group: absence of one or two signs of the signs above, but no scarlatiniform rash (test).
- Low-risk group: coryza, with no nodes, no swollen tonsils, and no scarlatiniform rash (no treatment, no test).

The absence of nodes, swollen tonsils, and scarlatiniform rash defined the low risk group.

The CDR derived by Smeesters et al. [21]

They used the signs and the symptoms recommended by the IDSA practice guidelines, which included viral signs (conjunctivitis, coryza, cough, diarrhea, viral-like exanthema) and bacterial or GAS signs (fever >38.5°C, tender cervical node, headache, petechiae on the palate, abdominal pain and sudden onset <12 hours). Age, viral and bacterial signs had β values of 2.8, 0.8 and 1.0 respectively:

- Age: ≤35 months (20 pts), 36-59 months (6 pts), ≥60 months (2 points)
- Viral signs: none (0 pt), 1 sign (7 pts), ≥2 signs (10 pts)
- Bacterial signs: none (10 pts), 1 sign (-2 pts), ≥2 signs (-2 pts)

The score was calculated for each patient. If bacteriological diagnosis was unavailable, a patient with a score ≥8 received symptomatic treatment and a patient with a score <8 received antibiotic treatment. If bacteriological diagnosis was available, the patient received:

- score <5: antibiotic,

- score 5-7: antibiotic if positive culture,
- score ≥8: symptomatic treatment.

A score ≥ 8 defined the low risk group.

The CDR derived by Joachim et al. [22]

They simplified the CDR derived by Smeesters et al. to use only 9 variables. Patients received one positive point for each bacterial sign (tender cervical node, headache, petechiae on the palate, abdominal pain and sudden onset <12 hours) and one negative point for each viral sign (conjunctivitis, coryza and diarrhea). They also received points for age (≤35 months: 1 point, 36-59 months: 2 points, ≥60 months: 3 points). If no bacteriologic diagnosis was available, symptomatic treatment was given for a score ≤2 and antibiotics for a score ≥3. If bacteriologic diagnosis was available, the patient received:

- score ≤2: no RDT, symptomatic treatment,
- score=3: RDT and antibiotics if positive,
- score ≥4: no RDT, antibiotics.

A score ≤ 2 defined the low risk group.

BMJ open

Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001482.R1
Article Type:	Research
Date Submitted by the Author:	15-Nov-2012
Complete List of Authors:	Le Marechal, Flore; CHU Lille, Lille Nord de France University, Pediatric Emergency and Infectious Disease Unit Martinot, Alain; CHU Lille, Lille Nord de France University, Pediatric Emergency and Infectious Disease Unit; Lille Nord de France University, EA2694, Epidemiology, Public Health and Quality of Care Alain, Duhamel; Lille Nord-de-France University, EA2694, Epidemiology, Public Health and Quality of Care; CHU Lille, Lille Nord de France University, Department of Biostatistics and Public Health Pruvost, Isabelle; CHU Lille, Lille Nord de France University, Pediatric Emergency and Infectious Disease Unit Dubos, Francois; CHU Lille, Lille Nord de France University, Pediatric Emergency and Infectious Disease Unit; Lille Nord de France University, EA2694, Epidemiology, Public Health and Quality of Care
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	General practice / Family practice, Infectious diseases, Epidemiology, Emergency medicine, Ear, nose and throat/otolaryngology
Keywords:	Paediatric A&E and ambulatory care < PAEDIATRICS, Paediatric infectious disease & immunisation < PAEDIATRICS, Epidemiology < INFECTIOUS DISEASES, Paediatric otolaryngology < OTOLARYNGOLOGY

Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables

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Funding: none

Conflict of interest: none

ARTICLE SUMMARY

Article focus

- Pharyngitis is a frequent diagnosis in children leading to excessive antibiotic treatments by the inability to distinguish a bacterial and viral cause of the disease despite the availability of rapid diagnostic test, too rarely done in children with pharyngitis.
- Several studies have analyzed the performance of clinical signs and developed clinical decision rules for the diagnosis of group A streptococcal (GAS) pharyngitis in children.
- Through a meta-analysis, this article focus on the methodological quality of these studies and on the value of clinical signs and decision rules that could be helpful to focus rapid diagnostic test to the children with higher risk of GAS pharyngitis.

Key messages

- No symptom considered alone is predictive enough of GAS pharyngitis.
- Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children, but are not performing enough for the positive diagnosis of GAS pharyngitis.
- Clinical decision rules could help clinicians to focus rapid diagnostic tests to children with high risk of GAS pharyngitis to reduce the use of antibiotic.

Strength and limitations

- Meta-analysis of all relevant articles, from 1975 to 2010 that analyzed the performance of clinical signs and derived or validated clinical decision rules for the diagnosis if GAS pharyngitis in children.
- A decision rule that performed as well as most rapid diagnostic tests to rule out GAS pharyngitis in children was identified, but has not been validated until now.
- Comparison between studies was limited by methodological weaknesses and heterogeneity between patients.

ABSTRACT

Objective: To identify the best clinical decision rules (CDRs) for diagnosing group A streptococcal (GAS) pharyngitis in children. A combination of symptoms could help clinicians to exclude GAS infection in children with pharyngitis.

Design: Systematic review and meta-analysis of original articles, which derived or validated a CDR in children. The Pubmed, OVID, INIST and Cochrane databases from 1975 to 2010. The databases were screened for articles that derived or validated a CDR on a pediatric population: 171 references were identified.

Setting: Any reference including primary care for children with pharyngitis.

Data extraction: The methodological quality of the articles selected was analyzed according to published quality standards. A meta-analysis was performed to assess the statistical performance of the CDRs and their variables for the diagnosis of GAS pharyngitis.

Primary outcome measure: The main criterion was a false-negative rate in the whole population not any worse than that of a rapid diagnostic test strategy for all patients (high sensitivity, low negative likelihood ratio).

Results Four derived and 12 validated CDRs for this diagnosis in children. These articles involved 10,523 children (mean age, 7 years; mean prevalence of GAS pharyngitis, 34%). No single variable was sufficient for diagnosis. Among the CDRs, that of Joachim et al. had a negative likelihood ratio of 0.3 (95%CI: 0.2-0.5), resulting in a post-test probability of 13%, which leads to 3.6% false-negative rate among low-risk patients and 10.8% overall, equivalent to that of some rapid diagnostic tests.

Conclusion The rule of Joachim et al. could be useful for clinicians who do not use rapid diagnostic tests and should allow avoiding antibiotic treatment for the 35% of children identified by the rule as not having GAS pharyngitis. It could thus lead to a more rational use of rapid diagnostic tests for those children at higher risk of GAS pharyngitis.

Trial registration: no

Introduction

Acute pharyngitis is one of the most common diseases in the world. It is diagnosed annually in 11 million patients in US emergency departments (ED) and other outpatient settings [1] and is responsible for more than 140 physician office visits and 96 antibiotic prescriptions per 1000 US children under 15 years of age [2]. The group A streptococcal (GAS) form is identified in 20 to 37% of children with pharyngitis [3,4].

The priority over the past 50 years has been the prevention of GAS complications such as local suppurations, invasive infections, and acute rheumatic fever (ARF). These complications are rare in industrialized countries, however; among children treated with antibiotics in GAS pharyngitis, less than 1% have suppurative complications [5], 3/100,000 have invasive infections [6] and 0.08 to 0.15/100,000 ARF [7,8]. ARF rates were declining even before the use of antibiotics because non-rheumatogenic types of streptococci were replacing the rheumatogenic types [9]. The prevention of these complications, however, has induced the large-scale prescription of antibiotics, which in turn might induce drug side-effects and the emergence of multidrug-resistant organisms due to pressure on the ecosystem [10].

National guidelines are different one country to another [11]. To optimize the use of antibiotics, in 2002 the Infectious Diseases Society of America (IDSA) recommended the use of pharyngeal swabs to take samples for bacterial cultures or rapid diagnostic tests (RDT) when physicians cannot clinically rule out a bacterial cause of the pharyngitis [12]. These recommendations have changed some medical practices, but adhesion remains partial [13]. Although diagnostic performances of RDT are good (sensitivity [Se], 85-90%, specificity [Sp], 90-100%) [14,15], they are still not widespread used [16], are offered to less than 50% of patients with pharyngitis [17], and antibiotic prescriptions for children with pharyngitis remain excessive in industrialized countries [2]. Moreover, RDT are not recommended in

practice in all settings internationally [18]. Clinical decision rules (CDRs) have been proposed to help physicians decide whether or not the patient needs further tests (RDT or culture) or direct antibiotic treatment without further testing. The IDSA recommends the use of such CDRs [12]. Although several authors have suggested CDRs for children [19-24], most of these have been validated only partially [25-36].

The aim of this study is to conduct the first systematic review, including a meta-analysis, of these CDRs and their variables for the diagnosis of GAS pharyngitis in children, to identify CDRs not any worse than that of a rapid diagnostic test strategy.

Methods

Search strategy and study selection criteria

This systematic search and quality assessment of studies was performed independently by FL and FD in august 2010. To identify eligible original articles, we searched four electronic databases: Medline via PubMed, INIST (Institute for Scientific and Technical Information) at article@inist, database now accessible at www.Refdoc.fr, the OVID library at http://ovidsp.ovid.com/, and the Cochrane library. In the Medline search, we used the medical subject heading terms "pharyngitis" (MeSH, restricted to major topic) and "predictive value of tests" (MeSH), separated by the Boolean operator AND. Limits were set to specify "human" as the species, "all child" as the age, and year of publication from 1975 to 2010, without limits on language of publication. In the other databases only the MeSH term "pharyngitis" was used and less limits to broaden the research: in INIST via Refdoc, we used the terms "pharyngitis" and "children" from 1975 to 2010; in OVID, we used the terms "pharyngitis", "children" and "sensitivity" with limits set to specify "clinical medicine" as journal subset, and year of publication from 1975 to 2010; in the Cochrane library, we used the term "pharyngitis" alone without limits of dates.

The study selection criterion was the presence of original data used to derive or validate a CDR for predicting GAS pharyngitis in a pediatric population. We reviewed the titles of all articles identified by electronic searches and then the abstracts of those that appeared eligible. Related articles and references in the articles that met the selection criterion were examined to identify references that our electronic research might have missed. Eligible articles were fully reviewed.

Quality criteria for the CDR derivation and validation studies

The quality of the selected articles was determined by applying the methodological standards of Wasson et al. [37] and Laupacis et al. [38]. Two of the authors (FL, FD) separately screened each article for the 10 criteria listed below. Each criterion applied to GAS pharyngitis was split into 1 to 4 items (one point per item), as detailed below. Derivation studies could have up to 24 items and validation studies 21. The criteria were:

(i) The outcome for the selected articles was GAS pharyngitis. It should have been defined and diagnosed with the gold standard, a throat culture. The culture technique should have been specified. The test used as the gold standard should have been assessed blinded, without knowledge of the value of the predictive variables. (ii) The predictive values used in the studies that derived each CDR should have been exhaustively identified and well defined, to facilitate its reproducible use. The choice of the variables should have been explained, and the potentially important variables not included should have been mentioned. The studies that validated CDRs should have used the predictive variables as listed and defined in the derivation. Analysis should have been performed blinded to the outcome. (iii) Important patient characteristics should have been described, e.g., age, sex ratio and any characteristics that might cause the predictive value to differ within the cohort of patients, such as the prevalence of GAS pharyngitis. (iv) The study site should have been specified, including the

medical setting and the country. (v) The statistics used to derive the CDRs should have been described and justified. The authors should have assessed the possibility that the logistic regression model overfitted the data [38]. (vi) The statistical performance of the CDRs should have been described. (vii) The reproducibility of the predictive variables and of the CDR should have been assessed. (viii) The study should have been prospective, and the CDR should have been fully validated, in accordance with recommendations [39]: derivation study, internal validation, external validation, and prospective study of the rule's impact on clinical behavior. (ix) The CDR should be clinically sensible, easy to use (simple and quick) and should suggest a course of action rather than a probability of disease. (x) The effects of clinical use should have been prospectively measured. This last criterion (impact of the CDR) was evaluated at point viii.

Main criteria of CDR performance

The aim of a CDR strategy is to identify a group of children at low risk of GAS pharyngitis to allow them to avoid antibiotic treatment for these patients and to propose an action (e.g., RDT) for patients classified in the high-risk group. A strategy including a CDR was considered useful if it did not increase the false negative rate in the overall population (high and low risk patients), compared to a RDT strategy for all patients (Figure 1). The RDT strategy (median Se: 89%, median Sp: 96%) has a median false negative rate of 11% [14]. Therefore, our criteria for evaluating the performance of each CDR were a Se as good as that of RDTs and a probability of GAS pharyngitis in the low-risk group of patients <11%. This corresponds to a negative likelihood ratio (LR–) of 0.2 or less when the prevalence of GAS pharyngitis is 30% [3, 4]. In the literature, a LR– under 0.2 is considered useful [38] and the median LR– for RDTs is 0.15 [14].

Statistical analysis

After the identification of the CDRs, the entire population was described, in percentages and 95% confidence intervals (CI) for dichotomous variables and means and ranges for continuous variables. The absence of the raw data prevented us from calculating the standard deviations. The statistical performance of the variables and the CDRs was analyzed for pediatric studies only and not in studies that included both children and adults. When possible, we focused on children older than 3 years [27], because younger children rarely have GAS pharyngitis [12].

The meta-analysis of the variables included in the CDRs and their validations used the DerSimonian and Laird method [41]. For the Se, Sp, positive and negative predictive values (PPV and NPV), we tested the heterogeneity between studies, applying the likelihood ratio test. For the odds ratio (OR), positive likelihood ratio (LR+) and LR–, we used Cochran's Q test. In analyses with significant heterogeneity or with four or more studies, a random effect model was used to assign the weight of each study. Pooled Se, Sp, PPV, NPV, LR+, LR– and OR with their 95% CIs were calculated for CDRs and their variables.

CDRs in the literature propose different courses of action according to the individual's clinical risk of GAS pharyngitis. In the selected studies, four CDRs proposed a course of action based on three levels of probability of GAS pharyngitis: high risk (antibiotics), intermediate risk (culture and antibiotics if positive), and low risk (no culture, no antibiotics). One CDR proposed a course of action based on two risk groups [20], and two CDRs offered four or five risk groups without any courses of action [19,25]. We chose to identify the CDRs with a useful LR– that would allow us to rule out GAS pharyngitis, as most second-generation RDTs do. Therefore we dichotomized each population into two groups: the low-risk group on one side and the intermediate and high-risk group on the other side (see supplementary material).

Results

Search strategy results

After excluding duplicates, our search strategy identified 65 references from PubMed, another 89 from INIST, 8 from OVID and 9 from the Cochrane database (see flowchart, Figure 2). Reading the titles and abstracts of these 171 references led us to exclude 150 articles that did not meet the inclusion criterion. Complete reading of the remaining 21 articles and reviewing their references, related articles and authors' publications identified 15 additional relevant references. Of these 36 references, 18 were excluded because they did not report the derivation or validation of a CDR on a pediatric population. In the 18 articles that fulfilled the inclusion criterion, six studies derived CDRs [19-24], and 12 validated them in children [25-36]. Of these 18 studies, the article cited as the source from which the World Health Organization's (WHO) CDR [20] was derived did not provide details about it, and the CDR by Centor et al. [19] used for validation in children was derived on adult patients. These two derivation studies were thus screened for methodological quality, but were excluded from the meta-analysis. However, the studies that validated these two CDRs among children [28-31] were included in the meta-analysis.

Patient characteristics

The 16 studies with data for children included 10,523 children. Eleven studies took place in industrialized countries and five in emerging countries. Nine studies were conducted in hospitals or clinics, six in pediatricians' or general practitioners' (GPs) offices, and one in GPs' offices and an ED. Overall, the derivation studies that could be reviewed (n=4) included 963 children (mean number per study: 241, range: 90–356) [21-24]. All the validation studies (n=12) together included 9,560 children (mean number per study: 797, range: 79–1,848) [25-

36]. The mean prevalence of GAS pharyngitis was 34% (median: 34%, range: 24–58%) and did not differ between the derivation and validation studies (33% vs. 34%; p=0.54) or between industrialized and emerging countries (34% vs. 33%; p=0.30). The children's mean age was 7 years, 5.9 in the derivation and 7.2 in the validation sets, 5.7 in the emerging and 8.4 in the industrialized countries. The studies used different inclusion criteria: “pharyngitis” (n=5) [23,24,27,35,36], “suspected GAS pharyngitis” (n=4) [22,26,29,34], “sore throat” (n=3) [28,31,33], “new upper respiratory tract infection” (n=2) [21,25] and both “new upper respiratory tract infection” and “sore throat” (n=2) [30,32].

Methodological quality for derivation and validation studies

Overall, the derivation studies correctly followed a median of 65% of the quality criteria (range: 13-83%). The derivation of WHO’s CDR was not found. The validation studies correctly followed a mean of 69% of these quality criteria (range: 43-86%) (Table 1).

One study used an RDT as the gold standard [24], and two others used RDTs or throat culture [29,34]. No derivation studies defined a predictive variable; three validation studies did so for at least one variable (i.e., cervical lymph node [25,27,30], abnormal pharynx [25], exudate [30]), but 7/12 validation studies changed a variable (e.g., tender node for node, fever≥38°C for fever>38°C). All studies described the CDRs, although one modified it [36]. No study specifically described whether assessments were blinded, but for validation studies, we considered that a prospective study based on the culture result and without any RDT validated this item. One derivation study simplified a rule without reconducting the statistical analyses [24]. Only one study was retrospective [34].

Performance of the variables

The CDRs considered 17 variables in all, most frequently lymph nodes, exudate, age, fever and cough. The supplementary materials include a table describing the types of variables by CDR and the details of the CDRs. Table 2 presents the meta-analysis of the statistical

performance of these variables. “Node >1.5 cm”, “sore throat” and “no diarrhea” each had a LR– under 0.5. The sensitivity of these three variables exceeded 0.81, and their NPV exceeded 0.72. The statistical performance of “Node >1.5 cm” was not reproducible with the other “node” variables. “Scarlatiniform rash” had the highest LR+ (4.7) and OR (4.8). All other LR+ were less than 2.

Performance of the CDRs

After meta-analysis of the validation studies, three rules had high Se (99%, 95% and 88%) and NPVs (87 to 88%). However, the rules of McIsaac et al. and Attia et al. were not discriminative (Sp, 14% and 4%), and were negative for only 10% and 3% of the population respectively (Table 3). These rules were therefore not useful in clinical practice. The rule tested by Joachim et al. had one of the best LR– (Table 3), with a value of 0.3 (95% CI: 0.2-0.5), which should help clinicians to rule out the diagnosis of GAS pharyngitis. Application of this CDR brought the probability of GAS pharyngitis down from 34% to 13% when the score of the CDR is negative (Figure 3). The rule of Joachim et al. also had the best performance, with a Se of 88%, a post-test probability of 13% in 28% of the low-risk patients, and a Sp of 35% (95% CI: 30-40). This rule leads to a 3.6% false-negative rate in this low-risk population and 11.5% overall with an RDT strategy for the intermediate and high-risk patient groups and on the assumption that the RDT sensitivity was 89%.

Discussion

The large number of studies and CDRs proposed for the diagnosis of GAS pharyngitis is evidence of physicians' desire to improve their management of this common disease and to limit antibiotic prescriptions, bacterial resistance and costs. Our study shows how difficult it is to develop and validate an effective and useful CDR. We identified 16 articles that described the derivation or validation of seven CDRs for the diagnosis of GAS pharyngitis in

children. The meta-analysis confirmed, as others recently, [42] that symptoms alone were not sufficient to rule out this diagnosis. Examination of the statistical performance of the variables included in the CDRs showed that none had a significant positive (>5) or negative (<0.2) LR [40]. Two CDRs brought the post-test probability of GAS pharyngitis to around 10% [22,24]. Only the CDR of Joachim et al. was considered useful for clinical use to exclude GAS pharyngitis.

The poor performance of each of these variables requires comment. It might be due to the low specificity of some signs (such as rhinorrhea and cervical nodes), their subjectivity in children (sore throat), or a lack of definition. For these reasons, several variables might have been recorded differently from study to study and possibly within some studies. Because the individual variables predict GAS pharyngitis so poorly, researchers have suggested combining potential predictive variables within a CDR. Our systematic review of standards for the derivation of CDRs [37,38], however, shows that none of the studies followed all of the methodological quality criteria, in particular, the studies that derived CDRs did not. The construction of two CDRs was not available for methodological analysis [20,25,43]. A rule that proposed an empirical simplification of the Breese score, without following any methodological standards was not included [44]. Two other rules not specifically derived for children [19,21], have nonetheless been used for validation in a paediatric population [28,29,32-35], despite the methodological requirement that rules be applied only in populations with the same characteristics as those used in the derivation sets [39]. We also identified statistical biases. When a CDR is derived on a population, the validation set should not include members of the derivation set [21]. Moreover, the logistic regression model of multivariate analyses in some studies might have been overfitted [19,23]. Finally, the validation of a CDR may entail its refinement [24,36], which in turn requires a new validation. The CDRs with the lowest LR– in our meta-analysis were those of Attia et al. [22]

and Joachim et al [24], which brought the post-test probability of GAS pharyngitis down to 9 and 13% respectively. Nonetheless, the CDR by Attia et al. was validated only once [36] and was not discriminative for clinical practice. The rule developed by Joachim et al. performed best but has not been externally validated yet and requires the collection of nine variables for its application, which may limit its use in practice. Since CDRs were more useful than individual symptoms, they might help the clinicians who do not use RDTs in ruling out the diagnosis of GAS pharyngitis. The interquartile range of LR– for second-generation RDTs varies from 0.07 to 0.19 [14]. Thus the probability of GAS pharyngitis would have been reduced from 34% to a post-test probability of less than 10% for most RDTs [14,15]. Compared to this full RDT strategy, the CDR of Joachim et al. leads to a maximum 11.5% false-negative rate globally: 3.6% in the low-risk group of patients (28%) and 7.9% in the intermediate and high risk group (72%), if we assume a RDT strategy with 89% sensitivity (probably an underestimate in this group). Nevertheless, none of the CDRs included in this study reached the level of performance required to bring both the probability of GAS pharyngitis and the risk of a false negative test to less than 10%, as most RDTs do.

Our study has some limitations. Because of the lack of access to individual data, except from two authors who provided the complete set of data from their derivation study [23,24], we could only perform a meta-analysis of the pooled data. Moreover, the populations involved in our analysis were heterogeneous and difficult to compare. These differences concerned (i) the objective of the study, since some studies sought to validate a CDR while others tested RDTs [35] or serologic titers [28]; (ii) the inclusion criteria, which differed between CDRs and even within the same CDR; and (iii) the mean age of the patients, which might influence the prevalence of the disease and the type of symptoms [27]. The prevalence of the disease varied and could double between studies, as a result of differences in patients' ages [31] or study sites or because of a short study period when GAS might be more or less

prevalent [19,22,25]. Although prevalence did not influence sensitivity, specificity or the LRs of the variables, it might influence the choice of variables for building the CDR, especially when methodological standards are not adhered to closely. A spectrum bias is possible if reference standards were not performed in all patients of the included studies. Variables might be defined differently between studies of the same CDR, and one CDR might suggest a different course of action in different studies [36]. Another important variation may come from the definition of the disease (pharyngitis), which was not provided in the studies and which varies between countries [12,45]. We had to create artificial risk groups and courses of action for three CDRs, although they had not been derived for that purpose; our results thus cannot reflect exactly the performance of each risk group. Finally, a review was recently published on this subject but focused the literature research on the signs and symptoms of pharyngitis, when we focused it on CDRs. Findings were slightly different in terms of articles reviewed and not different in terms of performance of individual variables. The CDR by Attia et al. was identified by their systematic research but not the one by Joachim et al [42].

Lastly, we must question whether physicians will use a CDR at all for a well-known and usually banal disease. It might be useful for countries were the RDT use is not recommended in current practice [18]. It might also well interest the 50% of physicians who do not use RDTs at all [13,16,17]. It will do so only, however, if the CDR produces accurate results, is useful, is well validated and is easy to use. The heterogeneity of patients between studies might necessitate a validation and a comparison of available CDRs in a single pediatric population. Our results showed that one CDR has a performance that did not produce a false-negative rate for GAS pharyngitis higher than that of the RDT strategy [20]. The rule has only 35% Sp; but its use could avoid about 6 millions of antibiotic prescriptions in American children (< 15 y.o.) when considering that almost 20% of the 300 millions of people in the US are under 15 and that 96/1000 [2] receive an antibiotic for pharyngitis.

However an external validation in different resource settings may be warranted before generalization. After validation, this CDR might help physicians to focus RDTs on children at higher risk of GAS pharyngitis and therefore decrease antibiotic prescriptions for children in the low-risk group.

Contributors

Study concept and design; study supervision: FLM, FD, IP, AM.

Acquisition of data: FLM.

Analysis and interpretation of data; critical revision of the manuscript for important intellectual content: FLM, FD, AD, IP, AM.

Drafting of the manuscript: FLM, FD, AM.

Statistical analysis: FLM, FD, AD.

Le Marechal and Dubos (guarantor) have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosures none

Funding none

Competing interest none

Ethics approval No ethical approval was needed for this pooled data meta-analysis

Data sharing statement There is no additional data available

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Fig 1. Expected performance of a clinical decision rules strategy for group A streptococcal pharyngitis in children compared to the rapid diagnostic test strategy.

Fig 2. Identification of clinical decision rules for the diagnosis of group A Streptococcal pharyngitis by a systematic database search.

Fig 3. Post-test probability of the clinical decision rules (CDRs) for the low-risk group of patients compared with the performance of the rapid diagnostic tests on Fagan's nomogram. The pre-test probability considered (prevalence of the disease) was 34%.

Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables

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Funding: none

Conflict of interest: none

ARTICLE SUMMARY

Article focus

- Pharyngitis is a frequent diagnosis in children leading to excessive antibiotic treatments by the inability to distinguish a bacterial and viral cause of the disease despite the availability of rapid diagnostic test, too rarely done in children with pharyngitis.
- Several studies have analyzed the performance of clinical signs and developed clinical decision rules for the diagnosis of group A streptococcal (GAS) pharyngitis in children.
- Through a meta-analysis, this article focus on the methodological quality of these studies and on the value of clinical signs and decision rules that could be helpful to focus rapid diagnostic test to the children with higher risk of GAS pharyngitis.

Key messages

- No symptom considered alone is predictive enough of GAS pharyngitis.
- Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children, but are not performing enough for the positive diagnosis of GAS pharyngitis.
- Clinical decision rules could help clinicians to focus rapid diagnostic tests to children with high risk of GAS pharyngitis to reduce the use of antibiotic.

Strength and limitations

- Meta-analysis of all relevant articles, from 1975 to 2010 that analyzed the performance of clinical signs and derived or validated clinical decision rules for the diagnosis if GAS pharyngitis in children.
- A decision rule that performed as well as most rapid diagnostic tests to rule out GAS pharyngitis in children was identified, but has not been validated until now.
- Comparison between studies was limited by methodological weaknesses and heterogeneity between patients.

ABSTRACT

Objective: To identify the best clinical decision rules (CDRs) for diagnosing group A streptococcal (GAS) pharyngitis in children. A combination of symptoms could help clinicians to exclude GAS infection in children with pharyngitis.

Design: Systematic review and meta-analysis of original articles, which derived or validated a CDR in children. The Pubmed, OVID, INIST and Cochrane databases from 1975 to 2010. The databases were screened for articles that derived or validated a CDR on a pediatric population: 171 references were identified.

Setting: Any reference including primary care for children with pharyngitis.

Data extraction: The methodological quality of the articles selected was analyzed according to published quality standards. A meta-analysis was performed to assess the statistical performance of the CDRs and their variables for the diagnosis of GAS pharyngitis.

Primary outcome measure: The main criterion was a false-negative rate in the whole population not any worse than that of a rapid diagnostic test strategy for all patients (high sensitivity, low negative likelihood ratio).

Results Four derived and 12 validated CDRs for this diagnosis in children. These articles involved 10,523 children (mean age, 7 years; mean prevalence of GAS pharyngitis, 34%). No single variable was sufficient for diagnosis. Among the CDRs, that of Joachim et al. had a negative likelihood ratio of 0.3 (95%CI: 0.2-0.5), resulting in a post-test probability of 13%, which leads to 3.6% false-negative rate among low-risk patients and 10.8% overall, equivalent to that of some rapid diagnostic tests.

Conclusion The rule of Joachim et al. could be useful for clinicians who do not use rapid diagnostic tests and should allow avoiding antibiotic treatment for the 35% of children identified by the rule as not having GAS pharyngitis. It could thus lead to a more rational use of rapid diagnostic tests for those children at higher risk of GAS pharyngitis.

Trial registration: no

Introduction

Acute pharyngitis is one of the most common diseases in the world. It is diagnosed annually in 11 million patients in US emergency departments (ED) and other outpatient settings [1] and is responsible for more than 140 physician office visits and 96 antibiotic prescriptions per 1000 US children under 15 years of age [2]. The group A streptococcal (GAS) form is identified in 20 to 37% of children with pharyngitis [3,4].

The priority over the past 50 years has been the prevention of GAS complications such as local suppurations, invasive infections, and acute rheumatic fever (ARF). These complications are rare in industrialized countries, however; among children treated with antibiotics in GAS pharyngitis, less than 1% have suppurative complications [5], 3/100,000 have invasive infections [6] and 0.08 to 0.15/100,000 ARF [7,8]. ARF rates were declining even before the use of antibiotics because non-rheumatogenic types of streptococci were replacing the rheumatogenic types [9]. The prevention of these complications, however, has induced the large-scale prescription of antibiotics, which in turn might induce drug side-effects and the emergence of multidrug-resistant organisms due to pressure on the ecosystem [10].

National guidelines are different one country to another [11]. To optimize the use of antibiotics, in 2002 the Infectious Diseases Society of America (IDSA) recommended the use of pharyngeal swabs to take samples for bacterial cultures or rapid diagnostic tests (RDT) when physicians cannot clinically rule out a bacterial cause of the pharyngitis [12]. These recommendations have changed some medical practices, but adhesion remains partial [13]. Although diagnostic performances of RDT are good (sensitivity [Se], 85-90%, specificity [Sp], 90-100%) [14,15], they are still not widespread used [16], are offered to less than 50% of patients with pharyngitis [17], and antibiotic prescriptions for children with pharyngitis remain excessive in industrialized countries [2]. Moreover, RDT are not recommended in

practice in all settings internationally [18]. Clinical decision rules (CDRs) have been proposed to help physicians decide whether or not the patient needs further tests (RDT or culture) or direct antibiotic treatment without further testing. The IDSA recommends the use of such CDRs [12]. Although several authors have suggested CDRs for children [19-24], most of these have been validated only partially [25-36].

The aim of this study is to conduct the first systematic review, including a meta-analysis, of these CDRs and their variables for the diagnosis of GAS pharyngitis in children, to identify CDRs not any worse than that of a rapid diagnostic test strategy.

Methods

Search strategy and study selection criteria

This systematic search and quality assessment of studies was performed independently by FL and FD in august 2010. To identify eligible original articles, we searched four electronic databases: Medline via PubMed, INIST (Institute for Scientific and Technical Information) at article@inist, database now accessible at www.Refdoc.fr, the OVID library at http://ovidsp.ovid.com/, and the Cochrane library. In the Medline search, we used the medical subject heading terms "pharyngitis" (MeSH, restricted to major topic) and "predictive value of tests" (MeSH), separated by the Boolean operator AND. Limits were set to specify "human" as the species, "all child" as the age, and year of publication from 1975 to 2010, without limits on language of publication. In the other databases only the MeSH term "pharyngitis" was used and less limits to broaden the research: in INIST via Refdoc, we used the terms "pharyngitis" and "children" from 1975 to 2010; in OVID, we used the terms "pharyngitis", "children" and "sensitivity" with limits set to specify "clinical medicine" as journal subset, and year of publication from 1975 to 2010; in the Cochrane library, we used the term "pharyngitis" alone without limits of dates.

The study selection criterion was the presence of original data used to derive or validate a CDR for predicting GAS pharyngitis in a pediatric population. We reviewed the titles of all articles identified by electronic searches and then the abstracts of those that appeared eligible. Related articles and references in the articles that met the selection criterion were examined to identify references that our electronic research might have missed. Eligible articles were fully reviewed.

Quality criteria for the CDR derivation and validation studies

The quality of the selected articles was determined by applying the methodological standards of Wasson et al. [37] and Laupacis et al. [38]. Two of the authors (FL, FD) separately screened each article for the 10 criteria listed below. Each criterion applied to GAS pharyngitis was split into 1 to 4 items (one point per item), as detailed below. Derivation studies could have up to 24 items and validation studies 21. The criteria were:

(i) The outcome for the selected articles was GAS pharyngitis. It should have been defined and diagnosed with the gold standard, a throat culture. The culture technique should have been specified. The test used as the gold standard should have been assessed blinded, without knowledge of the value of the predictive variables. (ii) The predictive values used in the studies that derived each CDR should have been exhaustively identified and well defined, to facilitate its reproducible use. The choice of the variables should have been explained, and the potentially important variables not included should have been mentioned. The studies that validated CDRs should have used the predictive variables as listed and defined in the derivation. Analysis should have been performed blinded to the outcome. (iii) Important patient characteristics should have been described, e.g., age, sex ratio and any characteristics that might cause the predictive value to differ within the cohort of patients, such as the prevalence of GAS pharyngitis. (iv) The study site should have been specified, including the

medical setting and the country. (v) The statistics used to derive the CDRs should have been described and justified. The authors should have assessed the possibility that the logistic regression model overfitted the data [38]. (vi) The statistical performance of the CDRs should have been described. (vii) The reproducibility of the predictive variables and of the CDR should have been assessed. (viii) The study should have been prospective, and the CDR should have been fully validated, in accordance with recommendations [39]: derivation study, internal validation, external validation, and prospective study of the rule's impact on clinical behavior. (ix) The CDR should be clinically sensible, easy to use (simple and quick) and should suggest a course of action rather than a probability of disease. (x) The effects of clinical use should have been prospectively measured. This last criterion (impact of the CDR) was evaluated at point viii.

Main criteria of CDR performance

The aim of a CDR strategy is to identify a group of children at low risk of GAS pharyngitis to allow them to avoid antibiotic treatment for these patients and to propose an action (e.g., RDT) for patients classified in the high-risk group. A strategy including a CDR was considered useful if it did not increase the false negative rate in the overall population (high and low risk patients), compared to a RDT strategy for all patients (Figure 1). The RDT strategy (median Se: 89%, median Sp: 96%) has a median false negative rate of 11% [14]. Therefore, our criteria for evaluating the performance of each CDR were a Se as good as that of RDTs and a probability of GAS pharyngitis in the low-risk group of patients <11%. This corresponds to a negative likelihood ratio (LR–) of 0.2 or less when the prevalence of GAS pharyngitis is 30% [3, 4]. In the literature, a LR– under 0.2 is considered useful [38] and the median LR– for RDTs is 0.15 [14].

Statistical analysis

After the identification of the CDRs, the entire population was described, in percentages and 95% confidence intervals (CI) for dichotomous variables and means and ranges for continuous variables. The absence of the raw data prevented us from calculating the standard deviations. The statistical performance of the variables and the CDRs was analyzed for pediatric studies only and not in studies that included both children and adults. When possible, we focused on children older than 3 years [27], because younger children rarely have GAS pharyngitis [12].

The meta-analysis of the variables included in the CDRs and their validations used the DerSimonian and Laird method [41]. For the Se, Sp, positive and negative predictive values (PPV and NPV), we tested the heterogeneity between studies, applying the likelihood ratio test. For the odds ratio (OR), positive likelihood ratio (LR+) and LR–, we used Cochran's Q test. In analyses with significant heterogeneity or with four or more studies, a random effect model was used to assign the weight of each study. Pooled Se, Sp, PPV, NPV, LR+, LR– and OR with their 95% CIs were calculated for CDRs and their variables.

CDRs in the literature propose different courses of action according to the individual's clinical risk of GAS pharyngitis. In the selected studies, four CDRs proposed a course of action based on three levels of probability of GAS pharyngitis: high risk (antibiotics), intermediate risk (culture and antibiotics if positive), and low risk (no culture, no antibiotics). One CDR proposed a course of action based on two risk groups [20], and two CDRs offered four or five risk groups without any courses of action [19,25]. We chose to identify the CDRs with a useful LR– that would allow us to rule out GAS pharyngitis, as most second-generation RDTs do. Therefore we dichotomized each population into two groups: the low-risk group on one side and the intermediate and high-risk group on the other side (see supplementary material).

Results

Search strategy results

After excluding duplicates, our search strategy identified 65 references from PubMed, another 89 from INIST, 8 from OVID and 9 from the Cochrane database (see flowchart, Figure 2). Reading the titles and abstracts of these 171 references led us to exclude 150 articles that did not meet the inclusion criterion. Complete reading of the remaining 21 articles and reviewing their references, related articles and authors' publications identified 15 additional relevant references. Of these 36 references, 18 were excluded because they did not report the derivation or validation of a CDR on a pediatric population. In the 18 articles that fulfilled the inclusion criterion, six studies derived CDRs [19-24], and 12 validated them in children [25-36]. Of these 18 studies, the article cited as the source from which the World Health Organization's (WHO) CDR [20] was derived did not provide details about it, and the CDR by Centor et al. [19] used for validation in children was derived on adult patients. These two derivation studies were thus screened for methodological quality, but were excluded from the meta-analysis. However, the studies that validated these two CDRs among children [28-31] were included in the meta-analysis.

Patient characteristics

The 16 studies with data for children included 10,523 children. Eleven studies took place in industrialized countries and five in emerging countries. Nine studies were conducted in hospitals or clinics, six in pediatricians' or general practitioners' (GPs) offices, and one in GPs' offices and an ED. Overall, the derivation studies that could be reviewed (n=4) included 963 children (mean number per study: 241, range: 90–356) [21-24]. All the validation studies (n=12) together included 9,560 children (mean number per study: 797, range: 79–1,848) [25-

36]. The mean prevalence of GAS pharyngitis was 34% (median: 34%, range: 24–58%) and did not differ between the derivation and validation studies (33% vs. 34%; p=0.54) or between industrialized and emerging countries (34% vs. 33%; p=0.30). The children's mean age was 7 years, 5.9 in the derivation and 7.2 in the validation sets, 5.7 in the emerging and 8.4 in the industrialized countries. The studies used different inclusion criteria: “pharyngitis” (n=5) [23,24,27,35,36], “suspected GAS pharyngitis” (n=4) [22,26,29,34], “sore throat” (n=3) [28,31,33], “new upper respiratory tract infection” (n=2) [21,25] and both “new upper respiratory tract infection” and “sore throat” (n=2) [30,32].

Methodological quality for derivation and validation studies

Overall, the derivation studies correctly followed a median of 65% of the quality criteria (range: 13-83%). The derivation of WHO’s CDR was not found. The validation studies correctly followed a mean of 69% of these quality criteria (range: 43-86%) (Table 1).

One study used an RDT as the gold standard [24], and two others used RDTs or throat culture [29,34]. No derivation studies defined a predictive variable; three validation studies did so for at least one variable (i.e., cervical lymph node [25,27,30], abnormal pharynx [25], exudate [30]), but 7/12 validation studies changed a variable (e.g., tender node for node, fever≥38°C for fever>38°C). All studies described the CDRs, although one modified it [36]. No study specifically described whether assessments were blinded, but for validation studies, we considered that a prospective study based on the culture result and without any RDT validated this item. One derivation study simplified a rule without reconducting the statistical analyses [24]. Only one study was retrospective [34].

Performance of the variables

The CDRs considered 17 variables in all, most frequently lymph nodes, exudate, age, fever and cough. The supplementary materials include a table describing the types of variables by CDR and the details of the CDRs. Table 2 presents the meta-analysis of the statistical

performance of these variables. “Node >1.5 cm”, “sore throat” and “no diarrhea” each had a LR– under 0.5. The sensitivity of these three variables exceeded 0.81, and their NPV exceeded 0.72. The statistical performance of “Node >1.5 cm” was not reproducible with the other “node” variables. “Scarlatiniform rash” had the highest LR+ (4.7) and OR (4.8). All other LR+ were less than 2.

Performance of the CDRs

After meta-analysis of the validation studies, three rules had high Se (99%, 95% and 88%) and NPVs (87 to 88%). However, the rules of McIsaac et al. and Attia et al. were not discriminative (Sp, 14% and 4%), and were negative for only 10% and 3% of the population respectively (Table 3). These rules were therefore not useful in clinical practice. The rule tested by Joachim et al. had one of the best LR– (Table 3), with a value of 0.3 (95% CI: 0.2-0.5), which should help clinicians to rule out the diagnosis of GAS pharyngitis. Application of this CDR brought the probability of GAS pharyngitis down from 34% to 13% when the score of the CDR is negative (Figure 3). The rule of Joachim et al. also had the best performance, with a Se of 88%, a post-test probability of 13% in 28% of the low-risk patients, and a Sp of 35% (95% CI: 30-40). This rule leads to a 3.6% false-negative rate in this low-risk population and 11.5% overall with an RDT strategy for the intermediate and high-risk patient groups and on the assumption that the RDT sensitivity was 89%.

Discussion

The large number of studies and CDRs proposed for the diagnosis of GAS pharyngitis is evidence of physicians' desire to improve their management of this common disease and to limit antibiotic prescriptions, bacterial resistance and costs. Our study shows how difficult it is to develop and validate an effective and useful CDR. We identified 16 articles that described the derivation or validation of seven CDRs for the diagnosis of GAS pharyngitis in

children. The meta-analysis confirmed, as others recently, [42] that symptoms alone were not sufficient to rule out this diagnosis. Examination of the statistical performance of the variables included in the CDRs showed that none had a significant positive (>5) or negative (<0.2) LR [40]. Two CDRs brought the post-test probability of GAS pharyngitis to around 10% [22,24]. Only the CDR of Joachim et al. was considered useful for clinical use to exclude GAS pharyngitis.

The poor performance of each of these variables requires comment. It might be due to the low specificity of some signs (such as rhinorrhea and cervical nodes), their subjectivity in children (sore throat), or a lack of definition. For these reasons, several variables might have been recorded differently from study to study and possibly within some studies. Because the individual variables predict GAS pharyngitis so poorly, researchers have suggested combining potential predictive variables within a CDR. Our systematic review of standards for the derivation of CDRs [37,38], however, shows that none of the studies followed all of the methodological quality criteria, in particular, the studies that derived CDRs did not. The construction of two CDRs was not available for methodological analysis [20,25,43]. A rule that proposed an empirical simplification of the Breese score, without following any methodological standards was not included [44]. Two other rules not specifically derived for children [19,21], have nonetheless been used for validation in a paediatric population [28,29,32-35], despite the methodological requirement that rules be applied only in populations with the same characteristics as those used in the derivation sets [39]. We also identified statistical biases. When a CDR is derived on a population, the validation set should not include members of the derivation set [21]. Moreover, the logistic regression model of multivariate analyses in some studies might have been overfitted [19,23]. Finally, the validation of a CDR may entail its refinement [24,36], which in turn requires a new validation. The CDRs with the lowest LR– in our meta-analysis were those of Attia et al. [22]

and Joachim et al [24], which brought the post-test probability of GAS pharyngitis down to 9 and 13% respectively. Nonetheless, the CDR by Attia et al. was validated only once [36] and was not discriminative for clinical practice. The rule developed by Joachim et al. performed best but has not been externally validated yet and requires the collection of nine variables for its application, which may limit its use in practice. Since CDRs were more useful than individual symptoms, they might help the clinicians who do not use RDTs in ruling out the diagnosis of GAS pharyngitis. The interquartile range of LR– for second-generation RDTs varies from 0.07 to 0.19 [14]. Thus the probability of GAS pharyngitis would have been reduced from 34% to a post-test probability of less than 10% for most RDTs [14,15]. Compared to this full RDT strategy, the CDR of Joachim et al. leads to a maximum 11.5% false-negative rate globally: 3.6% in the low-risk group of patients (28%) and 7.9% in the intermediate and high risk group (72%), if we assume a RDT strategy with 89% sensitivity (probably an underestimate in this group). Nevertheless, none of the CDRs included in this study reached the level of performance required to bring both the probability of GAS pharyngitis and the risk of a false negative test to less than 10%, as most RDTs do.

Our study has some limitations. Because of the lack of access to individual data, except from two authors who provided the complete set of data from their derivation study [23,24], we could only perform a meta-analysis of the pooled data. Moreover, the populations involved in our analysis were heterogeneous and difficult to compare. These differences concerned (i) the objective of the study, since some studies sought to validate a CDR while others tested RDTs [35] or serologic titers [28]; (ii) the inclusion criteria, which differed between CDRs and even within the same CDR; and (iii) the mean age of the patients, which might influence the prevalence of the disease and the type of symptoms [27]. The prevalence of the disease varied and could double between studies, as a result of differences in patients' ages [31] or study sites or because of a short study period when GAS might be more or less

prevalent [19,22,25]. Although prevalence did not influence sensitivity, specificity or the LRs of the variables, it might influence the choice of variables for building the CDR, especially when methodological standards are not adhered to closely. A spectrum bias is possible if reference standards were not performed in all patients of the included studies. Variables might be defined differently between studies of the same CDR, and one CDR might suggest a different course of action in different studies [36]. Another important variation may come from the definition of the disease (pharyngitis), which was not provided in the studies and which varies between countries [12,45]. We had to create artificial risk groups and courses of action for three CDRs, although they had not been derived for that purpose; our results thus cannot reflect exactly the performance of each risk group. Finally, a review was recently published on this subject but focused the literature research on the signs and symptoms of pharyngitis, when we focused it on CDRs. Findings were slightly different in terms of articles reviewed and not different in terms of performance of individual variables. The CDR by Attia et al. was identified by their systematic research but not the one by Joachim et al [42].

Lastly, we must question whether physicians will use a CDR at all for a well-known and usually banal disease. It might be useful for countries were the RDT use is not recommended in current practice [18]. It might also well interest the 50% of physicians who do not use RDTs at all [13,16,17]. It will do so only, however, if the CDR produces accurate results, is useful, is well validated and is easy to use. The heterogeneity of patients between studies might necessitate a validation and a comparison of available CDRs in a single pediatric population. Our results showed that one CDR has a performance that did not produce a false-negative rate for GAS pharyngitis higher than that of the RDT strategy [20]. The rule has only 35% Sp; but its use could avoid about 6 millions of antibiotic prescriptions in American children (< 15 y.o.) when considering that almost 20% of the 300 millions of people in the US are under 15 and that 96/1000 [2] receive an antibiotic for pharyngitis.

However an external validation in different resource settings may be warranted before generalization. After validation, this CDR might help physicians to focus RDTs on children at higher risk of GAS pharyngitis and therefore decrease antibiotic prescriptions for children in the low-risk group.

Contributors

Study concept and design; study supervision: FLM, FD, IP, AM.

Acquisition of data: FLM.

Analysis and interpretation of data; critical revision of the manuscript for important intellectual content: FLM, FD, AD, IP, AM.

Drafting of the manuscript: FLM, FD, AM.

Statistical analysis: FLM, FD, AD.

Le Marechal and Dubos (guarantor) have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosures none

Funding none

Competing interest none

Ethics approval No ethical approval was needed for this pooled data meta-analysis

Data sharing statement There is no additional data available

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Fig 1. Expected performance of a clinical decision rules strategy for group A streptococcal pharyngitis in children compared to the rapid diagnostic test strategy.

Fig 2. Identification of clinical decision rules for the diagnosis of group A Streptococcal pharyngitis by a systematic database search.

Fig 3. Post-test probability of the clinical decision rules (CDRs) for the low-risk group of patients compared with the performance of the rapid diagnostic tests on Fagan's nomogram. The pre-test probability considered (prevalence of the disease) was 34%.

Table 1. Methodological Quality of the Selected Studies that Derived or Validated Clinical Decision Rules for the Diagnosis of Group A Streptococcal Pharyngitis in Children

Quality criteria [37,38]	Breese [25]	Funamura [26]	Karacan * [27]	Centor † [19]	Dagnelie [28]	Hall [29]	WHO † [20]	Steinhoff [30]	Rimoin [31]	McIsaac † [21]	McIsaac [32]	McIsaac [33]	Edmonson [34]	Tanz [35]	Attia † [22]	Attia [36]	Smeesters † [23]	Joachim † [24]
Children	670	892	857	0	79	561	MD	451	1810	90	167	454	1184	1848	297	587	220	356
/total population	/670	/892	/857	/234	/558	/561		/451	/1810	/521	/620	/787	/1184	/1848	/297	/587	/220	/356
Outcome																		
GAS pharyngitis	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
Culture	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	0
Culture described	0	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1
Blind assessment	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Variables																		
Defined	NC	NC	NC	0	NC	NC	0	NC	NC	0	NC	NC	NC	NC	0	NC	0	0
Choice explained	NC	NC	NC	0	NC	NC	0	NC	NC	0	NC	NC	NC	NC	0	NC	1	1
Important variables	NC	NC	NC	1	NC	NC	0	NC	NC	1	NC	NC	NC	NC	1	NC	0	0
Same variables	0	0	0	NC	0	0	NC	0	1	NC	0	1	1	1	NC	0	NC	NC
Blind assessment	1	1	1	0	0	0		1	1	0	1	0	1	0	0	1	0	0
Patients' characteristics																		
Age (years)	MD	0-16	MD	>15	4-14	2-17	MD	2-13	2-12	3-14	3-14	3-17	MD	3-18	0.5-18	MD	0-15	0-15
Mean/median age	MD	MD	5.6	MD	‖	9	MD	MD	5.1	‖	MD	‖	8.4¶	9.3	6.2	6.8	6.6	5.4
Sex ratio	MD	MD	1.2	MD	MD	0.9	MD	1.1	1.3	‖	‖	MD	0.9	0.9	1.1	1.0	1.3	1.1

Table 1 continued

Prevalence GAS (%)	54	28	49	||	58	27	MD	24	29	36	35	34	32	30	29	37	26	33
Study site																		
Medical setting	GP	clinic	hospital	ED	GP	ED, GP	MD	hospital	clinic	GP	GP	GP	clinic	GP	ED	ED	ED	ED
Country	US	US	TUR	US	NL**	US	MD	EG	BR,EG,HR	CA	CA	CA	US	US	US**	US**	BR	BR
Statistics																		
Described	NC	NC	NC	1	NC	NC	0	NC	NC	1	NC	NC	NC	NC	1	NC	1	1
Logistic regression	NC	NC	NC	1	NC	NC	0	NC	NC	1	NC	NC	NC	NC	1	NC	1	0
Outcome/variable	NC	NC	NC	0	NC	NC	0	NC	NC	1	NC	NC	NC	NC	1	NC	0	0
Performance described	0	1	1	0	1	1	0	1	1	1	1	1	1	1	0	1	1	1
CDR Reproducibility	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Development ††	3	3	3	1	3	3	0	3	3	2	3	3	0	3	1	3	2	2
CDR practical use																		
Clinically sensible	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Easy to use	0	0	0	1	1	1	1.	1	1	1	1	1	1	1	1	1	0	0
Course of action	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Total score:	9‡‡	12‡‡	13‡‡	14†	13‡‡	14‡‡	3†	16‡‡	18‡‡	20†	15‡‡	16‡‡	13‡‡	17‡‡	16†	16‡‡	17†	15†
N/24† or N/21‡‡ (%)	(43)	(57)	(62)	(58)	(62)	(67)	(13)	(76)	(86)	(83)	(71)	(76)	(62)	(81)	(67)	(76)	(71)	(63)

*children>3 years old only; † derivation studies; ||validated, but adult and pediatric data; ¶estimated with the number of children per age group; **not provided in the articles; †† development of the rule [37]: derivation study (1 point), internal validation (2 points), external and prospective validation (3 points) and impact of the rule on clinical behaviour (4 points); ‡‡: validation study. 1: validated; 0: not validated, although not specified; BR: Brazil; Ca: Canada; ED: emergency department; EG: Egypt; GAS: group A streptococcal; GP: general practitioner; HR: Croatia; MD: Missing data; NC: Not concerned; NL: Netherlands; TUR: Turkey; US: United States of America; WHO: World Health Organization.
Each study present criterion for patient characteristics and medical setting worth one point each.

Table 2. Meta-analysis of the Statistical Performance of the Predictive Variables for the Diagnosis of Group A Streptococcal Pharyngitis in Children

Variables	References	Pop (n)	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR– (95% CI)	OR (95%CI)
Positive symptoms									
Tender cervical node									
Node : any size	[22-24,29,30,34]	3067	45 (42-48)	71 (69-73)	40 (37-43)	76 (74-77)	1.6 (1.5-1.8)	0.7 (0.7-0.8)	2.3 (1.9-2.8)
Node > 1.5 cm	[30]	451	81 (73-88)	45 (40-50)	32 (26-37)	89 (83-92)	1.5 (1.3-1.7)	0.4 (0.3-0.6)	3.6 (2.1-6.1)
Node > 2 cm	[27]	857	40 (36-45)	78 (74-81)	63 (57-69)	58 (54-62)	1.8 (1.3-2.5)	0.8 (0.7-0.9)	2.4 (1.8-3.2)
Pharynx									
Abnormal pharynx	[27]	857	42 (37-46)	77 (72-80)	63 (57-68)	58 (54-62)	1.8 (1.3-2.5)	0.8 (0.6-0.9)	2.3 (1.7-3.1)
Pharyngeal exudate	[22,29,30]	1308	31 (26-36)	81 (78-83)	37 (32-42)	77 (74-79)	1.6 (1.3-1.9)	0.9 (0.8-0.9)	2.0 (1.5-2.6)
Swollen tonsils	[22,34]	1481	58 (54-63)	57 (54-60)	39 (35-42)	75 (72-78)	1.3 (1.2-1.5)	0.7 (0.7-0.8)	1.9 (1.5-2.3)
Fever									
History of fever (HF)	[29,30]	1006	70 (65-75)	32 (29-35)	26 (23-30)	76 (71-80)	1.1 (1.0-1.1)	0.9 (0.7-1.1)	1.2 (0.9-1.7)
Fever > 38°C	[22,27,30,34]	2789	53 (50-56)	56 (54-59)	40 (37-43)	68 (66-71)	1.1 (1.1-1.5)	0.9 (0.8-1.1)	1.3 (1.1-2.2)
Fever > 38,5°C	[23,24]	576	64 (57-70)	28 (24-33)	28 (24-32)	64 (57-70)	0.9 (0.8-1.0)	1.2 (1.0-1.6)	0.7 (0.5-1.1)
HF or >38°C	[22,27,29,30,34]	3795	56 (54-60)	49 (47-51)	35 (33-37)	70 (67-72)	1.1 (1.1-1.3)	0.9 (0.8-1.1)	1.3 (1.1-1.9)
Headeache	[22-24,27]	1730	51 (48-55)	64 (61-67)	48 (44-51)	67 (64-70)	1.3 (1.1-1.5)	0.9 (0.8-1.0)	1.5 (1.2-2.2)
Sore throat	[27,34]	2041	86 (83-88)	27 (25-30)	43 (41-46)	75 (71-78)	1.2 (1.1-1.2)	0.5 (0.4-0.6)	2.5 (2.0-3.2)
Scarlatiniform rash	[22]	297	14 (8-23)	97 (93-98)	63 (41-81)	74 (68-79)	4.7 (2.1-10.5)	0.9 (0.8-1.0)	4.8 (1.8-12.7)

Table 2 continued

Petechia on the palate	[22-24]	873	20 (16-25)	88 (86-91)	42 (34-51)	72 (69-75)	1.8 (1.3-2.5)	0.9 (0.9-1.0)	2.0 (1.3-2.9)
Sudden onset	[23,25]	576	32 (26-39)	69 (65-74)	31 (25-38)	70 (65-74)	1.1 (0.8-1.4)	1.0 (0.9-1.1)	1.1 (0.7-1.6)
Negative symptoms									
No cough	[23,24,27,29,30,34]	3627	65 (63-68)	55 (53-57)	43 (41-45)	75 (73-77)	1.5 (1.4-1.7)	0.6 (0.6-0.7)	2.4 (2.1-3.1)
No rhinorrhea	[22-24,27,30,34]	3365	71 (69-74)	50 (48-52)	43 (41-45)	76 (74-79)	1.3 (1.3-1.5)	0.6 (0.6-0.8)	2.2 (1.9-3.3)
No abdominal pain	[22-24]	873	69 (64-75)	29 (26-33)	30 (26-33)	69 (64-74)	1.0 (0.9-1.1)	1.1 (0.8-1.3)	1.0 (0.7-1.3)
No diarrhea	[23,24,27]	1433	94 (92-95)	12 (10-14)	43 (40-45)	72 (65-79)	1.1 (1.0-1.1)	0.5 (0.3-0.7)	2.3 (1.5-3.4)
No conjonctivitis	[23,24]	576	100 (NC-100)	6 (4-8)	32 (28-36)	100 (NC-100)	1.0 (1.0-1.0)	NC	NC
No viral exanthema	[23,24]	576	88 (83-92)	2 (1-3)	28 (25-32)	22 (11-38)	1.0 (1.0-1.0)	8.4 (3.2-21.6)	0.1 (0.0-0.3)

Pop: population; n: number of children; Se: sensitivity; CI: confidence interval; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; OR: odds ratio; NC: not calculable

PPV and NPV should be interpreted with the prevalence of the disease in each study, available in Table 1.

Table 3. Meta-analysis of the Statistical Performance of Validation Studies of Clinical Decision Rules for Group A Streptococcal Pharyngitis in Children (Low vs. Intermediate and High Risk)

Initial CDR (First author)	Reference	Children /total	Se (95%CI)	Sp (95%CI)	PPV (95%CI)	NPV (95%CI)	LR+ (95%CI)	LR– (95%CI)	OR (95%CI)	% of patients at low risk
Breese	[25-27]	2419/2419	63 (60-66)	83 (81-85)	74 (71-77)	76 (73-78)	3.2 (2.8-3.6)	0.7 (0.6-0.7)	7.6 (6.2-9.3)	64
Centor	[28,29]	640/1119	41 (34-48)	85 (81-88)	55 (47-62)	76 (72-80)	2.0 (1.6-2.7)	0.8 (0.7-0.8)	3.2 (2.1-4.8)	77
McIsaac	[32-35]	3187/3652	95 (94-96)	14 (13-15)	33 (32-35)	87 (83-90)	1.1 (1.0-1.1)	0.4 (0.3-0.5)	3.2 (2.3-4.4)	10
WHO	[30,31]	2261/2261	6 (4-8)	96 (95-97)	37 (28-46)	73 (71-75)	1.6 (1.1-2.4)	1.0 (1.0-1.0)	1.6 (1.1-2.5)	95
Attia	[36]	545/545	99 (97-100)	4 (3-7)	39 (35-44)	88 (66-97)	1.0 (1.0-1.1)	0.2 (0.1-0.9)	4.9 (1.1-21.5)	3
Smeesters	[23]	220/220	84 (73-91)	41 (34-49)	33 (26-41)	88 (79-94)	1.4 (1.2-1.7)	0.4 (0.2-0.7)	3.7 (1.7-8.1)	35
Joachim	[24]	576/576*	88 (82-92)	35 (30-40)	37 (33-42)	87 (81-91)	1.4 (1.2-1.5)	0.3 (0.2-0.5)	4.0 (2.4-6.6)	28

*Results that concerned the population of Smeesters et al. and Joachim et al.'s study
CDR: clinical decision rule; Se: sensitivity; CI: confidence interval; Sp: specificity; PPV: positive predictive value of the test; NPV: negative predictive value of the test; LR+: positive likelihood ratio; LR–: negative likelihood ratio; OR: Odds ratio; NC: not calculable.
The thresholds for low-risk groups were: Breese: score ≤ 29 (18-29); Centor: score ≤ 2 (0-2); McIsaac: score ≤ 1 (0-1); WHO: absence of ADP and exudate; Attia: 0 symptoms; Smeesters: score ≥ 8; Joachim: score ≤ 2 (0-2)

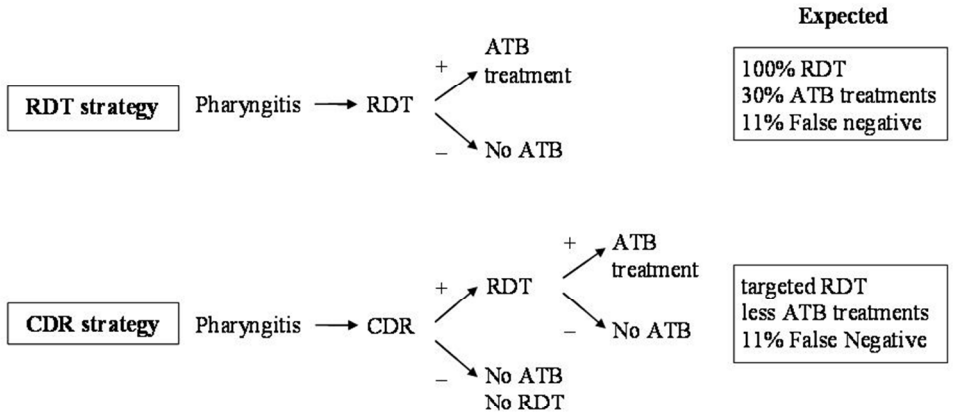
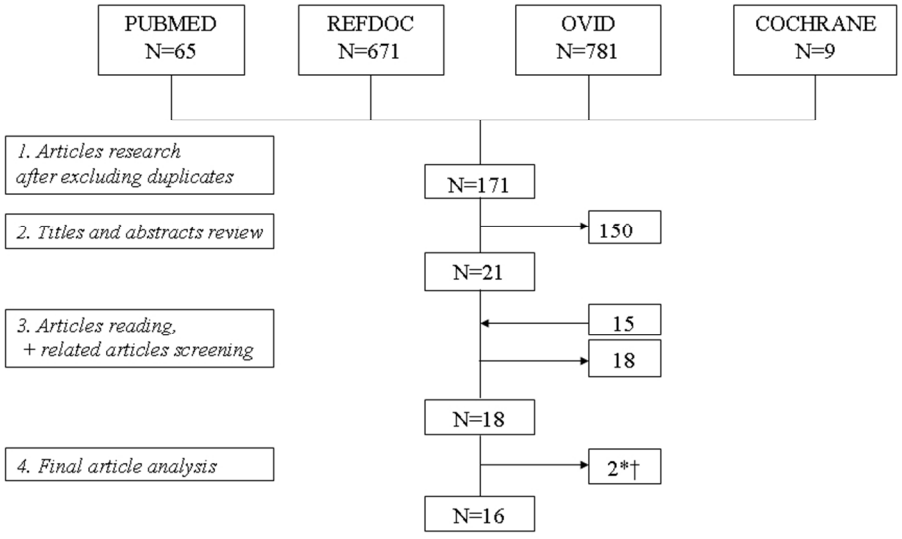


Figure 1.

Figure 1. Expected performance of a clinical decision rules strategy for group A streptococcal pharyngitis in children compared to the rapid diagnostic test strategy

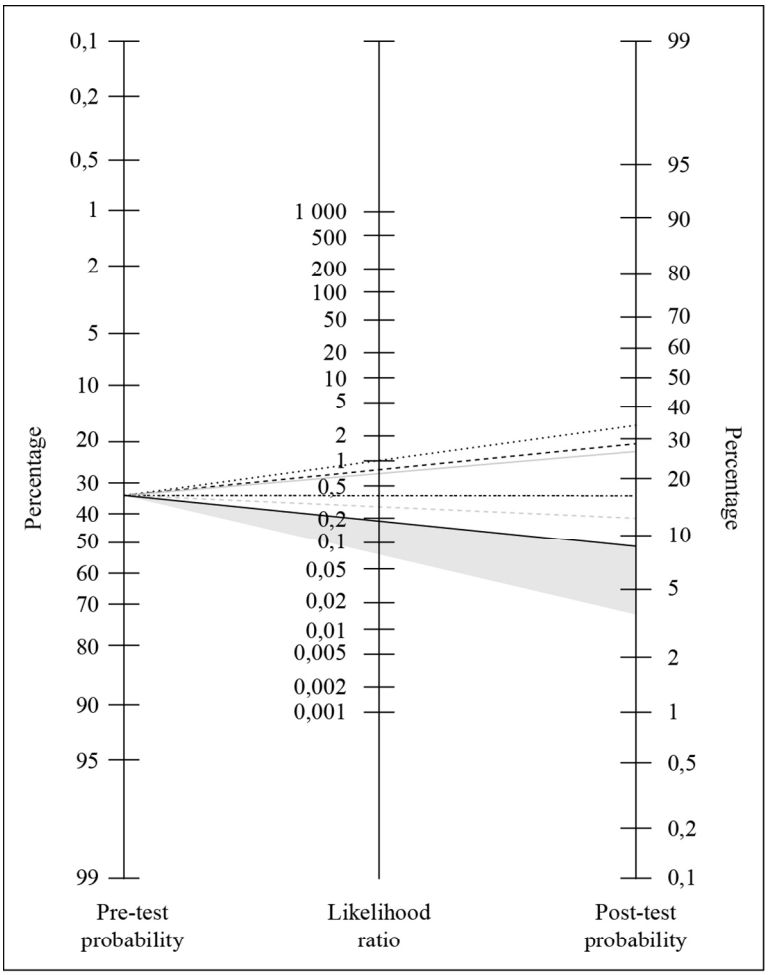
ATB, Antibiotics; CDR, Clinical Decision Rules; RDT, Rapid Diagnostic Test

254x190mm (96 x 96 DPI)



* An excluded CDR, derived in an adult population but validated twice in children, was considered for the methodological quality analysis (19).
† The derivation study of a CDR was not available for analysis [14].

Identification of clinical decision rules for the diagnosis of group A Streptococcal pharyngitis by a systematic database search.
254x190mm (96 x 96 DPI)



··· WHO's CDR (post-test probability of 34%)
-- The CDR of Centor et al. (post-test probability of 29%)
The CDR of Breese et al. (post-test probability of 27%)
·-·- The CDR of McIsaac et al. and Smeesters et al. (post-test probability of 17%)
-·- The CDR of Joachim et al. (post-test probability of 13%)
— The CDR of Attia et al. (post-test probability of 9%)
25-75th quartiles for Rapid Diagnostic Tests [13]

Post-test probability of the clinical decision rules (CDRs) for the low-risk group of patients compared with the performance of the rapid diagnostic tests on Fagan's nomogram. The pre-test probability considered (prevalence of the disease) was 34%.
190x288mm (150 x 150 DPI)

Supplementary material

Variables in the Clinical Decision Rules (CDRs) for the Diagnosis of Group A Streptococcal Pharyngitis and Description of these CDRs

Table. Variables of the CDRs Derived for the Diagnosis of Group A Streptococcal Pharyngitis.

Variables	Breese [23]	Centor* [17]	WHO [18]	McIsaac [19]	Attia [20]	Smeesters [21]	Joachim [22]
Cervical lymph nodes	X	X	X	X	X	X	X
Pharyngeal exudate†	X	X	X	X	X		
Age	X			X		X	X
Fever	≥38°C	X#		>38°C		>38.5°C	
Cough	X	X		X		X	
Headache	X					X	X
Sore throat	X						
Sudden onset						X	X
Abdominal pain						X	X
Conjunctivitis						X	X
Diarrhea						X	X
Coryza					X	X	X
Petechia on the palate						X	X
Viral exanthema						X	
Scarlatiniform rash					X		
Month	X						
White blood cell count	X						

*Rule derived in adult patients but validated twice in children
†pharyngeal or tonsillar exudates or swelling
#History of fever

Each CDR is detailed below. The low risk group as determined from identified studies is underlined at the bottom of each CDR.

The CDR derived by Breese et al. [23]

Predictive variable	Points assigned		
Age (years)			
2 or under	1		
3, 15 or more	2		
4, 11 to 14	3		
5 to 10	4		
Months			
July, August, September	1		
June, October, November	2		
January, May, December	3		
February, March, April	4		
Signs and symptoms	**Yes**	**No**	**Unknown**
Fever ≥ 100.5 F	4	2	2
Sore throat	4	2	2
Cough	2	4	4
Headache	4	2	2
Abnormal Pharynx	4	1	3
Abnormal Cervical glands	4	2	3
White blood count			
0-8.4	1		
8.5-10.4	2		
10.5-13.4	3		
13.5-20.4	5		
20.5 or more	6		
Not done	3		

For each patient, they recorded 9 variables, assigned points to each of them, calculated the score and did a throat culture. They created 4 groups: patients with less than 50% risk of GAS pharyngitis were assigned to the groups “no” or “maybe no”; patients with more than 50% were assigned in the groups “yes” or “maybe yes”. A score ≤ 29 defined the low risk group.

The CDR derived by Centor et al. [17]

They derived the CDR on adults. Four of 11 signs and symptoms were statistically correlated with a positive GAS culture: swollen tender anterior cervical node, tonsillar exudates, fever history and lack of cough. Each variable was worth one point. The 5 probability groups had an increasing prevalence of GAS pharyngitis. A score ≤ 2 defined the low risk group.

The CDR derived by the WHO [18]

The WHO recommended in a book that "a child who has tender, enlarged lymph nodes in the front of the neck, and a white exudate on the throat is classified as having streptococcal sore throat". The absence of both clinical signs defined the low risk group.

The CDR derived by McIsaac et al. [19]

The CDR was derived on children and adults. Five of 23 variables were statistically associated with GAS pharyngitis: age, temperature >38°C, no cough, tender anterior cervical adenopathy and swollen tonsils or exudate. Each variable was worth one point. To adjust for age, children aged 3 to 14 years were assigned 1 point, those aged 15 to 44 received a score of 0 and those aged 45 or more received a score of -1. If the total score was :

- 0 or 1: no culture or antibiotic required.
- 2 or 3: culture and antibiotic if positive.
- 4 or 5: culture and antibiotic if positive.

A score ≤ 1 defined the low risk group.

The CDR derived by Attia et al. [20]

Four of the 12 clinical variables screened were statistically associated with GAS pharyngitis: coryza, swollen tonsils, tender enlarged nodes and scarlatiniform rash. Patients were split into 3 probability groups:

- High-risk group: enlarged nodes, swollen tonsils, no coryza with or without scarlatiniform rash (treat, no test).
- Moderate-risk group: absence of one or two signs of the signs above, but no scarlatiniform rash (test).
- Low-risk group: coryza, with no nodes, no swollen tonsils, and no scarlatiniform rash (no treatment, no test).

The absence of nodes, swollen tonsils, and scarlatiniform rash defined the low risk group.

The CDR derived by Smeesters et al. [21]

They used the signs and the symptoms recommended by the IDSA practice guidelines, which included viral signs (conjunctivitis, coryza, cough, diarrhea, viral-like exanthema) and bacterial or GAS signs (fever >38.5°C, tender cervical node, headache, petechiae on the palate, abdominal pain and sudden onset <12 hours). Age, viral and bacterial signs had β values of 2.8, 0.8 and 1.0 respectively:

- Age: ≤35 months (20 pts), 36-59 months (6 pts), ≥60 months (2 points)
- Viral signs: none (0 pt), 1 sign (7 pts), ≥2 signs (10 pts)
- Bacterial signs: none (10 pts), 1 sign (-2 pts), ≥2 signs (-2 pts)

The score was calculated for each patient. If bacteriological diagnosis was unavailable, a patient with a score ≥8 received symptomatic treatment and a patient with a score <8 received antibiotic treatment. If bacteriological diagnosis was available, the patient received:

- score <5: antibiotic,

- score 5-7: antibiotic if positive culture,
- score ≥8: symptomatic treatment.

A score ≥ 8 defined the low risk group.

The CDR derived by Joachim et al. [22]

They simplified the CDR derived by Smeesters et al. to use only 9 variables. Patients received one positive point for each bacterial sign (tender cervical node, headache, petechiae on the palate, abdominal pain and sudden onset <12 hours) and one negative point for each viral sign (conjunctivitis, coryza and diarrhea). They also received points for age (≤35 months: 1 point, 36-59 months: 2 points, ≥60 months: 3 points). If no bacteriologic diagnosis was available, symptomatic treatment was given for a score ≤2 and antibiotics for a score ≥3. If bacteriologic diagnosis was available, the patient received:

- score ≤2: no RDT, symptomatic treatment,
- score=3: RDT and antibiotics if positive,
- score ≥4: no RDT, antibiotics.

A score ≤ 2 defined the low risk group.

14-Nov-2012
Manuscript ID bmjopen-2012-001482 entitled *"Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables"* submitted to BMJ Open,

Dear Mr. Richard Sands, Managing Editor,
BMJ Open rsands@bmjgroup.com

Please find below our point-by-point answers for the editor's and reviewers' comments.
We thank the editor and reviewers for their comments that have improved the quality of our manuscript. We hope that you will consider it suitable for publication.
Best regards.
F. Dubos

Editor's comments
Please include in the methods who did the searching and quality assessment of the studies.
Answer: The searching and quality assessment was performed independently by F Le Marechal and F Dubos. This information has been added in the Method section (p5, lines 11-12): *"This systematic search and quality assessment of studies was performed independently by FL and FD in august 2010."*

Reviewers' comments
Reviewer 1:
Robert Cohen
CHI Creteil, Pediatrics
Conflict of Interest None

This study is interesting, methodologically well conducted and well written. However, with the results observed, we can draw conclusions completely opposite of the authors. So that, various passages of the article need to be written to modulate the authors' conclusions.
Answer: It has been performed as recommended by the reviewer in the article summary, in the Abstract and in the conclusion.

Page 2 key message 2 « Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children » It is not true: the clinical decision rules perform as well rapid antigen test only for sensitivity and LR- not for specificity ant LR+. For example, the CDR of Joachim the Sp is of 35% (95% for rapid antigen test) and the LR+ is of 1.4 (10 to 20 for rapid antigen test). Recent European and US guidelines do no recommend the use of clinical rules for the management of pharyngitis in children.
Answer: We completely agree with the reviewer that LR+ of CDRs for pharyngitis is of poor interest. We also agree that recent US guidelines do not recommend the use of clinical rules for the management of pharyngitis in children. However, still a lot of unnecessary antibiotics are prescribed in this situation despite recommendations. Moreover, as mentioned by the other reviewer, rapid diagnostic tests are not recommended everywhere. For these reasons, the use of clinical rules to RULE OUT (i.e., low LR-) may be useful. A modification has been done to be more precise (p2, Key messages, 2nd bullet): *"Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children, but are not performing enough for the positive diagnosis of GAS pharyngitis."*

Strength and limitations, Second bullet point « A decision rule that performed as well as most rapid diagnostic tests was identified, but has not been validated until now » Same remark, it is not true for sensitivity and LR+ I suggest « A decision rule that performed as well as most rapid diagnostic tests in term of sensitivity and LHR - was identified, but has not been validated until now »

Answer: A modification has been done to be more precise about the ability of the decision rule to "rule out" the diagnosis and not "to rule in" (p2, Strength and limitations, 2nd bullet): *"A decision rule that performed as well as most rapid diagnostic tests to rule out GAS pharyngitis in children was identified, but has not been validated until now."*

Page 3, Abstract Objective: I suggest a modification « To identify the best clinical decision rules (CDRs) for diagnosing group A streptococcal (GAS) pharyngitis in children. A combination of symptoms could help clinicians to predict which cases of pharyngitis in children might be GAS infections. »

Answer: A modification has been done to be clearer (p3, Abstract, Objectives): *"A combination of symptoms could help clinicians to exclude GAS infection in children with pharyngitis."*

Conclusion « The rule of Joachim et al. could be useful for clinicians who are reluctant to use rapid diagnostic tests and should allow them avoid antibiotic treatment for children who do not have GAS pharyngitis." I think that it is not true, because very few proportion of patient (less than 30%) had had score sufficiently low to allow to not using rapid antigen test or culture.

Answer: We agree with the reviewer that the use of the best rule will avoid an antibiotic treatment for 35% of children with pharyngitis. Although it is only 35% (95%CI, 30-40), it is still a lot when considering that about 20% of the 300 millions of people in the US are under 15 and that 96/1000 [*McCaig et al, JAMA 2002*] receive an antibiotic for pharyngitis! It represents about 6 millions of antibiotic prescriptions that could be avoided only by the use of a good clinical decision rule in children and adolescents, and much more by the proper use of rapid diagnostic tests. To take into account the comment of the reviewer and to show the usefulness of a good clinical prediction rule in this situation, we have reformulated the 2 last sentences in the Abstract and the conclusion of the manuscript:

- Abstract (p3): *"The rule of Joachim et al. could be useful for clinicians who do not use rapid diagnostic tests and should allow them avoid antibiotic treatment for the 35% of children identified by the rule as not having GAS pharyngitis."*
- Conclusion (p15, lines 4-6): *"The rule has only 35% Sp; but its use could avoid about 6 millions of antibiotic prescriptions in American children (< 15 y.o.) when considering that almost 20% of the 300 millions of people in the US are under 15 and that 96/1000 [2] receive an antibiotic for pharyngitis."*

Reviewer: 2

Dr Carole Cummins
Senior Lecturer, School of Health and Population Sciences University of Birmingham

I have no competing interests.

I reviewed an earlier draft of this article and some of my previous points have been addressed. I said in my previous review however that the authors should make it clear that not all guidelines mandatory rapid tests, and although the authors have cited an article that

makes this point, it would be worth stating that rapid tests are not recommended practice in all settings internationally, as this implies that the purpose and use to which a decision rule is put may vary. In some settings it would be used to improve diagnosis, but elsewhere might be used to reduce or replace tests. Authors could consider citing the guidelines as well as the review article. While this is perhaps not necessary for publication, it would ensure that differences in practice internationally are made clear.

Answer: We agree with this remark of the reviewer and have raised this important issue both in the introduction (p4-5): *"Moreover, RDT are not recommended in practice in all settings internationally [18]."* and in the discussion section (p14, lines 22-23): *"It might be useful for countries were the RDT use is not recommended in current practice [18]."*

My main outstanding criticism however is that I had previously suggested that databases searched using the OVID platform and via INIST should be specified or the search strategy would be incomplete and unevaluable by the reader. This has not been addressed and is an important point as it influences the assessable quality of what otherwise appears to be a high quality systematic review. It also means that updating would be difficult should anyone wish to do this. For example, was Ebase searched or the Science Citation Index? This really should be clear and would improve a useful paper considerably from the systematic review aspect.

Answer: As recommended by the reviewer, we have provided details about our search strategy. The search has been done once again during this revision to ensure its reproducibility. A flow chart has been produced (Figure 2). Changes are available in the search strategy and study selection criteria section of the Methods (p5, lines 11-23): *"This systematic search and quality assessment of references was performed independently by FL and FD in august 2010. To identify eligible original articles, we searched four electronic databases: Medline via PubMed, INIST (Institute for Scientific and Technical Information) at article@inist, database now accessible at www.Refdoc.fr, the OVID library at http://ovidsp.ovid.com/, and the Cochrane library. In the Medline search, we used the medical subject heading terms "pharyngitis" (MeSH, restricted to major topic) and "predictive value of tests" (MeSH), separated by the Boolean operator AND. Limits were set to specify "human" as the species, "all child" as the age, and year of publication from 1975 to 2010, without limits on language of publication. In the other databases only the MeSH term "pharyngitis" was used and less limits to broaden the research: in INIST via Refdoc, we used the terms "pharyngitis" and "children" from 1975 to 2010; in OVID, we used the terms "pharyngitis", "children" and "sensitivity" with limits set to specify "clinical medicine" as journal subset, and year of publication from 1975 to 2010; in the Cochrane library, we used the term "pharyngitis" alone without limits of dates."*

Search dates should also be added.

Answer: It was already provided for the PubMed search and has been added for the other electronic databases. If the reviewer talks about the date when the search has been performed, it has been added in the search strategy section of the Methods (p5, lines 11-12): *"This systematic search and quality assessment of studies was performed independently by FL and FD in august 2010."*

Also on review methods: -A flowchart of citations might be expected in the supplementary material. Ideally text as well as MESH terms would have been used.

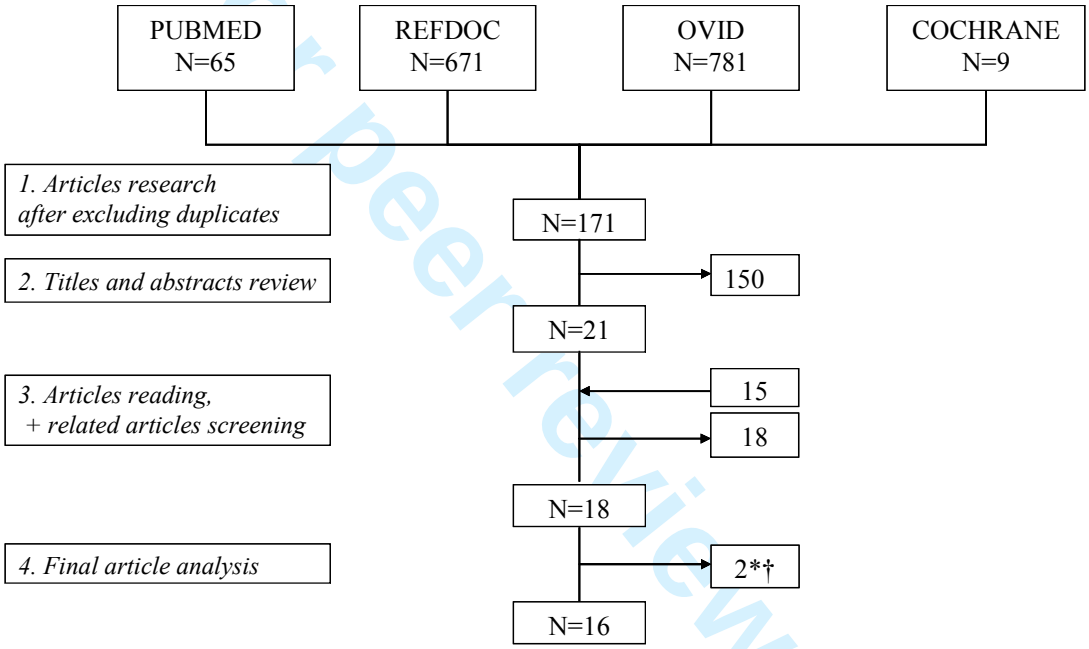
Answer: The flow chart has been added as recommended (Figure 2). For terms that corresponded to MESH terms (used but not mentioned indeed), the information (MESH) has been added (p5, lines 16, 17, 19): *"In the Medline search, we used the medical subject*

heading terms "pharyngitis" (MeSH, restricted to major topic) and "predictive value of tests" (MeSH), separated by the Boolean operator AND."

There's a typo – "avec" instead of "have".
Answer: The error has been corrected in the Article summary section, p2.

Results are credible as long as more information on the databases searched is provided.
Answer: We think to have now answered to this question (see previously).

A flow chart would be desirable.
Answer: The flowchart has been added.



* An excluded CDR, derived in an adult population but validated twice in children, was considered for the methodological quality analysis (19).
† The derivation study of a CDR was not available for analysis [14].

Fig 2. Identification of clinical decision rules for the diagnosis of group A Streptococcal pharyngitis by a systematic database search.

Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001482.R2
Article Type:	Research
Date Submitted by the Author:	21-Dec-2012
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	General practice / Family practice, Infectious diseases, Epidemiology, Emergency medicine, Ear, nose and throat/otolaryngology
Keywords:	Paediatric A&E and ambulatory care < PAEDIATRICS, Paediatric infectious disease & immunisation < PAEDIATRICS, Epidemiology < INFECTIOUS DISEASES, Paediatric otolaryngology < OTOLARYNGOLOGY

Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables

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Funding: none

Conflict of interest: none

ARTICLE SUMMARY

Article focus

- Pharyngitis is a frequent diagnosis in children leading to excessive antibiotic treatments by the inability to distinguish a bacterial and viral cause of the disease despite the availability of rapid diagnostic test, too rarely done in children with pharyngitis.
- Several studies have analyzed the performance of clinical signs and developed clinical decision rules for the diagnosis of group A streptococcal (GAS) pharyngitis in children.
- Through a meta-analysis, this article focus on the methodological quality of these studies and on the value of clinical signs and decision rules that could be helpful to focus rapid diagnostic test to the children with higher risk of GAS pharyngitis.

Key messages

- No symptom considered alone is predictive enough of GAS pharyngitis.
- Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children, but are not performing enough for the positive diagnosis of GAS pharyngitis, which can lead to a still important antibiotic prescription level.
- Therefore, clinical decision rules could be used to focus rapid diagnostic tests to children with high risk of GAS pharyngitis to reduce the use of antibiotic.

Strength and limitations

- Meta-analysis of all relevant articles, from 1975 to 2010 that analyzed the performance of clinical signs and derived or validated clinical decision rules for the diagnosis if GAS pharyngitis in children.
- A decision rule that performed as well as most rapid diagnostic tests to rule out GAS pharyngitis in children was identified, but has not been validated until now.

- Comparison between studies was limited by methodological weaknesses and heterogeneity between patients.

ABSTRACT

Objective: To identify the best clinical decision rules (CDRs) for diagnosing group A streptococcal (GAS) pharyngitis in children. A combination of symptoms could help clinicians to exclude GAS infection in children with pharyngitis.

Design: Systematic review and meta-analysis of original articles involving CDRs in children. The Pubmed, OVID, INIST and Cochrane databases from 1975 to 2010 were screened for articles that derived or validated a CDR on a pediatric population: 171 references were identified.

Setting: Any reference including primary care for children with pharyngitis.

Data extraction: The methodological quality of the articles selected was analyzed according to published quality standards. A meta-analysis was performed to assess the statistical performance of the CDRs and their variables for the diagnosis of GAS pharyngitis.

Primary outcome measure: The main criterion was a false-negative rate in the whole population not any worse than that of a rapid diagnostic test strategy for all patients (high sensitivity, low negative likelihood ratio).

Results Four derived and 12 validated CDRs for this diagnosis in children. These articles involved 10,523 children (mean age, 7 years; mean prevalence of GAS pharyngitis, 34%). No single variable was sufficient for diagnosis. Among the CDRs, that of Joachim et al. had a negative likelihood ratio of 0.3 (95%CI: 0.2-0.5), resulting in a post-test probability of 13%, which leads to 3.6% false-negative rate among low-risk patients and 10.8% overall, equivalent to rapid diagnostic tests in some studies.

Conclusion The rule of Joachim et al. could be useful for clinicians who do not use rapid diagnostic tests and should allow avoiding antibiotic treatment for the 35% of children identified by the rule as not having GAS pharyngitis. Due to its poor specificity, such CDR should be used to focus rapid diagnostic tests to children with high risk of GAS pharyngitis to reduce the antibiotic consumption.

Trial registration: no

Introduction

Acute pharyngitis is one of the most common diseases in the world. It is diagnosed annually in 11 million patients in US emergency departments (ED) and other outpatient settings [1] and is responsible for more than 140 physician office visits and 96 antibiotic prescriptions per 1000 US children under 15 years of age [2]. The group A streptococcal (GAS) form is identified in 20 to 37% of children with pharyngitis [3,4].

The priority over the past 50 years has been the prevention of GAS complications such as local suppurations, invasive infections, and acute rheumatic fever (ARF). These complications are rare in industrialized countries, however; among children treated with antibiotics in GAS pharyngitis, less than 1% have suppurative complications [5], 3/100,000 have invasive infections [6] and 0.08 to 0.15/100,000 ARF [7,8]. ARF rates were declining even before the use of antibiotics because non-rheumatogenic types of streptococci were replacing the rheumatogenic types [9]. The prevention of these complications, however, has induced the large-scale prescription of antibiotics, which in turn might induce drug side-effects and the emergence of multidrug-resistant organisms due to pressure on the ecosystem [10].

National guidelines are different one country to another [11]. To optimize the use of antibiotics, in 2012 the Infectious Diseases Society of America (IDSA) recommended the use of pharyngeal swabs to take samples for bacterial cultures or rapid diagnostic tests (RDT) because the clinical features alone do not reliably discriminate between GAS and viral pharyngitis [12]. These recommendations have changed some medical practices, but adhesion remains partial [13]. Although diagnostic performances of RDT are good (sensitivity [Se], 85-90%, specificity [Sp], 90-100%) [14,15], they are still not widespread used [16], are offered to less than 50% of patients with pharyngitis [17], and antibiotic prescriptions for children with pharyngitis remain excessive in industrialized countries [2]. Moreover, RDT are not

recommended in practice in all settings internationally [18]. Clinical decision rules (CDRs) have been proposed to help physicians decide whether or not the patient needs further tests (RDT or culture) or direct antibiotic treatment without further testing. The IDSA recommends the use of such CDRs [12]. Although several authors have suggested CDRs for children [19-24], most of these have been validated only partially [25-36].

The aim of this study is to conduct the first systematic review, including a meta-analysis, of these CDRs and their variables for the diagnosis of GAS pharyngitis in children, to identify CDRs not any worse than that of a rapid diagnostic test strategy.

Methods

Search strategy and study selection criteria

This systematic search and quality assessment of studies was performed independently by FL and FD in august 2010. To identify eligible original articles, we searched four electronic databases: Medline via PubMed, INIST (Institute for Scientific and Technical Information) at article@inist, database now accessible at www.Refdoc.fr, the OVID library at http://ovidsp.ovid.com/, and the Cochrane library. In the Medline search, we used the medical subject heading terms "pharyngitis" (MeSH, restricted to major topic) and "predictive value of tests" (MeSH), separated by the Boolean operator AND. Limits were set to specify "human" as the species, "all child" as the age, and year of publication from 1975 to 2010, without limits on language of publication. In the other databases only the MeSH term "pharyngitis" was used and less limits to broaden the research: in INIST via Refdoc, we used the terms "pharyngitis" and "children" from 1975 to 2010; in OVID, we used the terms "pharyngitis", "children" and "sensitivity" with limits set to specify "clinical medicine" as journal subset, and year of publication from 1975 to 2010; in the Cochrane library, we used the term "pharyngitis" alone without limits of dates.

The study selection criterion was the presence of original data used to derive or validate a CDR for predicting GAS pharyngitis in a pediatric population. We reviewed the titles of all articles identified by electronic searches and then the abstracts of those that appeared eligible. Related articles and references in the articles that met the selection criterion were examined to identify references that our electronic research might have missed. Eligible articles were fully reviewed.

Quality criteria for the CDR derivation and validation studies

The quality of the selected articles was determined by applying the methodological standards of Wasson et al. [37] and Laupacis et al. [38]. Two of the authors (FL, FD) separately screened each article for the 10 criteria listed below. Each criterion applied to GAS pharyngitis was split into 1 to 4 items (one point per item), as detailed below. Derivation studies could have up to 24 items and validation studies 21. The criteria were:

(i) The outcome for the selected articles was GAS pharyngitis. It should have been defined and diagnosed with the gold standard, a throat culture. The culture technique should have been specified. The test used as the gold standard should have been assessed blinded, without knowledge of the value of the predictive variables. (ii) The predictive values used in the studies that derived each CDR should have been exhaustively identified and well defined, to facilitate its reproducible use. The choice of the variables should have been explained, and the potentially important variables not included should have been mentioned. The studies that validated CDRs should have used the predictive variables as listed and defined in the derivation. Analysis should have been performed blinded to the outcome. (iii) Important patient characteristics should have been described, e.g., age, sex ratio and any characteristics that might cause the predictive value to differ within the cohort of patients, such as the prevalence of GAS pharyngitis. (iv) The study site should have been specified, including the

medical setting and the country. (v) The statistics used to derive the CDRs should have been described and justified. The authors should have assessed the possibility that the logistic regression model overfitted the data [38]. (vi) The statistical performance of the CDRs should have been described. (vii) The reproducibility of the predictive variables and of the CDR should have been assessed. (viii) The study should have been prospective, and the CDR should have been fully validated, in accordance with recommendations [39]: derivation study, internal validation, external validation, and prospective study of the rule's impact on clinical behavior. (ix) The CDR should be clinically sensible, easy to use (simple and quick) and should suggest a course of action rather than a probability of disease. (x) The effects of clinical use should have been prospectively measured. This last criterion (impact of the CDR) was evaluated at point viii.

Main criteria of CDR performance

The aim of a CDR strategy is to identify a group of children at low risk of GAS pharyngitis to allow them to avoid antibiotic treatment for these patients and to propose an action (e.g., RDT) for patients classified in the high-risk group. A strategy including a CDR was considered useful if it did not increase the false negative rate in the overall population (high and low risk patients), compared to a RDT strategy for all patients (Figure 1). The RDT strategy (median Se: 89%, median Sp: 96%) has a median false negative rate of 11% [14]. Therefore, our criteria for evaluating the performance of each CDR were a Se as good as that of RDTs and a probability of GAS pharyngitis in the low-risk group of patients <11%. This corresponds to a negative likelihood ratio (LR–) of 0.2 or less when the prevalence of GAS pharyngitis is 30% [3, 4]. In the literature, a LR– under 0.2 is considered useful [38] and the median LR– for RDTs is 0.15 [14].

Statistical analysis

After the identification of the CDRs, the entire population was described, in percentages and 95% confidence intervals (CI) for dichotomous variables and means and ranges for continuous variables. The absence of the raw data prevented us from calculating the standard deviations. The statistical performance of the variables and the CDRs was analyzed for pediatric studies only and not in studies that included both children and adults. When possible, we focused on children older than 3 years [27], because younger children rarely have GAS pharyngitis [12].

The meta-analysis of the variables included in the CDRs and their validations used the DerSimonian and Laird method [41]. For the Se, Sp, positive and negative predictive values (PPV and NPV), we tested the heterogeneity between studies, applying the likelihood ratio test. For the odds ratio (OR), positive likelihood ratio (LR+) and LR–, we used Cochran's Q test. In analyses with significant heterogeneity or with four or more studies, a random effect model was used to assign the weight of each study. Pooled Se, Sp, PPV, NPV, LR+, LR– and OR with their 95% CIs were calculated for CDRs and their variables.

CDRs in the literature propose different courses of action according to the individual's clinical risk of GAS pharyngitis. In the selected studies, four CDRs proposed a course of action based on three levels of probability of GAS pharyngitis: high risk (antibiotics), intermediate risk (culture and antibiotics if positive), and low risk (no culture, no antibiotics). One CDR proposed a course of action based on two risk groups [20], and two CDRs offered four or five risk groups without any courses of action [19,25]. We chose to identify the CDRs with a useful LR– that would allow us to rule out GAS pharyngitis, as most second-generation RDTs do. Therefore we dichotomized each population into two groups: the low-risk group on one side and the intermediate and high-risk group on the other side (see supplementary material).

Results

Search strategy results

After excluding duplicates, our search strategy identified 65 references from PubMed, another 89 from INIST, 8 from OVID and 9 from the Cochrane database (see flowchart, Figure 2). Reading the titles and abstracts of these 171 references led us to exclude 150 articles that did not meet the inclusion criterion. Complete reading of the remaining 21 articles and reviewing their references, related articles and authors' publications identified 15 additional relevant references. Of these 36 references, 18 were excluded because they did not report the derivation or validation of a CDR on a pediatric population. In the 18 articles that fulfilled the inclusion criterion, six studies derived CDRs [19-24], and 12 validated them in children [25-36]. Of these 18 studies, the article cited as the source from which the World Health Organization's (WHO) CDR [20] was derived did not provide details about it, and the CDR by Centor et al. [19] used for validation in children was derived on adult patients. These two derivation studies were thus screened for methodological quality, but were excluded from the meta-analysis. However, the studies that validated these two CDRs among children [28-31] were included in the meta-analysis.

Patient characteristics

The 16 studies with data for children included 10,523 children. Eleven studies took place in industrialized countries and five in emerging countries. Nine studies were conducted in hospitals or clinics, six in pediatricians' or general practitioners' (GPs) offices, and one in GPs' offices and an ED. Overall, the derivation studies that could be reviewed (n=4) included 963 children (mean number per study: 241, range: 90–356) [21-24]. All the validation studies (n=12) together included 9,560 children (mean number per study: 797, range: 79–1,848) [25-

36]. The mean prevalence of GAS pharyngitis was 34% (median: 34%, range: 24–58%) and did not differ between the derivation and validation studies (33% vs. 34%; p=0.54) or between industrialized and emerging countries (34% vs. 33%; p=0.30). The children's mean age was 7 years, 5.9 in the derivation and 7.2 in the validation sets, 5.7 in the emerging and 8.4 in the industrialized countries. The studies used different inclusion criteria: “pharyngitis” (n=5) [23,24,27,35,36], “suspected GAS pharyngitis” (n=4) [22,26,29,34], “sore throat” (n=3) [28,31,33], “new upper respiratory tract infection” (n=2) [21,25] and both “new upper respiratory tract infection” and “sore throat” (n=2) [30,32].

Methodological quality for derivation and validation studies

Overall, the derivation studies correctly followed a median of 65% of the quality criteria (range: 13-83%). The derivation of WHO’s CDR was not found. The validation studies correctly followed a mean of 69% of these quality criteria (range: 43-86%) (Table 1).

One study used an RDT as the gold standard [24], and two others used RDTs or throat culture [29,34]. No derivation studies defined a predictive variable; three validation studies did so for at least one variable (i.e., cervical lymph node [25,27,30], abnormal pharynx [25], exudate [30]), but 7/12 validation studies changed a variable (e.g., tender node for node, fever≥38°C for fever>38°C). All studies described the CDRs, although one modified it [36]. No study specifically described whether assessments were blinded, but for validation studies, we considered that a prospective study based on the culture result and without any RDT validated this item. One derivation study simplified a rule without reconducting the statistical analyses [24]. Only one study was retrospective [34].

Performance of the variables

The CDRs considered 17 variables in all, most frequently lymph nodes, exudate, age, fever and cough. The supplementary materials include a table describing the types of variables by CDR and the details of the CDRs. Table 2 presents the meta-analysis of the statistical

performance of these variables. “Node >1.5 cm”, “sore throat” and “no diarrhea” each had a LR– under 0.5. The sensitivity of these three variables exceeded 0.81, and their NPV exceeded 0.72. The statistical performance of “Node >1.5 cm” was not reproducible with the other “node” variables. “Scarlatiniform rash” had the highest LR+ (4.7) and OR (4.8). All other LR+ were less than 2.

Performance of the CDRs

After meta-analysis of the validation studies, three rules had high Se (99%, 95% and 88%) and NPVs (87 to 88%). However, the rules of McIsaac et al. and Attia et al. were not discriminative (Sp, 14% and 4%), and were negative for only 10% and 3% of the population respectively (Table 3). These rules were therefore not useful in clinical practice. The rule tested by Joachim et al. had one of the best LR– (Table 3), with a value of 0.3 (95% CI: 0.2-0.5), which should help clinicians to rule out the diagnosis of GAS pharyngitis. Application of this CDR brought the probability of GAS pharyngitis down from 34% to 13% when the score of the CDR is negative (Figure 3). The rule of Joachim et al. also had the best performance, with a Se of 88%, a post-test probability of 13% in 28% of the low-risk patients, and a Sp of 35% (95% CI: 30-40). This rule leads to a 3.6% false-negative rate in this low-risk population and 11.5% overall with an RDT strategy for the intermediate and high-risk patient groups and on the assumption that the RDT sensitivity was 89%.

Discussion

The large number of studies and CDRs proposed for the diagnosis of GAS pharyngitis is evidence of physicians' desire to improve their management of this common disease and to limit antibiotic prescriptions, bacterial resistance and costs. Our study shows how difficult it is to develop and validate an effective and useful CDR. We identified 16 articles that described the derivation or validation of seven CDRs for the diagnosis of GAS pharyngitis in

children. The meta-analysis confirmed, as others recently, [42] that symptoms alone were not sufficient to rule out this diagnosis. Examination of the statistical performance of the variables included in the CDRs showed that none had a significant positive (>5) or negative (<0.2) LR [40]. Two CDRs brought the post-test probability of GAS pharyngitis to around 10% [22,24]. Only the CDR of Joachim et al. was considered useful for clinical use to exclude GAS pharyngitis.

The poor performance of each of these variables requires comment. It might be due to the low specificity of some signs (such as rhinorrhea and cervical nodes), their subjectivity in children (sore throat), or a lack of definition. For these reasons, several variables might have been recorded differently from study to study and possibly within some studies. Because the individual variables predict GAS pharyngitis so poorly, researchers have suggested combining potential predictive variables within a CDR. Our systematic review of standards for the derivation of CDRs [37,38], however, shows that none of the studies followed all of the methodological quality criteria, in particular, the studies that derived CDRs did not. The construction of two CDRs was not available for methodological analysis [20,25,43]. A rule that proposed an empirical simplification of the Breese score, without following any methodological standards was not included [44]. Two other rules not specifically derived for children [19,21], have nonetheless been used for validation in a paediatric population [28,29,32-35], despite the methodological requirement that rules be applied only in populations with the same characteristics as those used in the derivation sets [39]. We also identified statistical biases. When a CDR is derived on a population, the validation set should not include members of the derivation set [21]. Moreover, the logistic regression model of multivariate analyses in some studies might have been overfitted [19,23]. Finally, the validation of a CDR may entail its refinement [24,36], which in turn requires a new validation. The CDRs with the lowest LR– in our meta-analysis were those of Attia et al. [22]

and Joachim et al [24], which brought the post-test probability of GAS pharyngitis down to 9 and 13% respectively. Nonetheless, the CDR by Attia et al. was validated only once [36] and was not discriminative for clinical practice. The rule developed by Joachim et al. performed best but has not been externally validated yet and requires the collection of nine variables for its application, which may limit its use in practice. Since CDRs were more useful than individual symptoms, they might help the clinicians who do not use RDTs in ruling out the diagnosis of GAS pharyngitis. The interquartile range of LR– for second-generation RDTs varies from 0.07 to 0.19 [14]. Thus the probability of GAS pharyngitis would have been reduced from 34% to a post-test probability of less than 10% for most RDTs [14,15]. Compared to this full RDT strategy, the CDR of Joachim et al. leads to a maximum 11.5% false-negative rate globally: 3.6% in the low-risk group of patients (28%) and 7.9% in the intermediate and high risk group (72%), if we assume a RDT strategy with 89% sensitivity (probably an underestimate in this group). Nevertheless, none of the CDRs included in this study reached the level of performance required to bring both the probability of GAS pharyngitis and the risk of a false negative test to less than 10%, as most RDTs do.

Our study has some limitations. Because of the lack of access to individual data, except from two authors who provided the complete set of data from their derivation study [23,24], we could only perform a meta-analysis of the pooled data. Moreover, the populations involved in our analysis were heterogeneous and difficult to compare. These differences concerned (i) the objective of the study, since some studies sought to validate a CDR while others tested RDTs [35] or serologic titers [28]; (ii) the inclusion criteria, which differed between CDRs and even within the same CDR; and (iii) the mean age of the patients, which might influence the prevalence of the disease and the type of symptoms [27]. The prevalence of the disease varied and could double between studies, as a result of differences in patients' ages [31] or study sites or because of a short study period when GAS might be more or less

prevalent [19,22,25]. Although prevalence did not influence sensitivity, specificity or the LRs of the variables, it might influence the choice of variables for building the CDR, especially when methodological standards are not adhered to closely. A spectrum bias is possible if reference standards were not performed in all patients of the included studies. Variables might be defined differently between studies of the same CDR, and one CDR might suggest a different course of action in different studies [36]. Another important variation may come from the definition of the disease (pharyngitis), which was not provided in the studies and which varies between countries [12,45]. We had to create artificial risk groups and courses of action for three CDRs, although they had not been derived for that purpose; our results thus cannot reflect exactly the performance of each risk group. Finally, a review was recently published on this subject but focused the literature research on the signs and symptoms of pharyngitis, when we focused it on CDRs. Findings were slightly different in terms of articles reviewed and not different in terms of performance of individual variables. The CDR by Attia et al. was identified by their systematic research but not the one by Joachim et al [42].

Lastly, we must question whether physicians will use a CDR at all for a well-known and usually banal disease. It might be useful for countries were the RDT use is not recommended in current practice [18]. It might also well interest the 50% of physicians who do not use RDTs at all [13,16,17]. It will do so only, however, if the CDR produces accurate results, is useful, is well validated and is easy to use. The heterogeneity of patients between studies might necessitate a validation and a comparison of available CDRs in a single pediatric population. Our results showed that one CDR has a performance that did not produce a false-negative rate for GAS pharyngitis higher than that of the RDT strategy [20]. The rule has only 35% Sp; but its use could avoid about 6 millions of antibiotic prescriptions in American children (< 15 y.o.) when considering that almost 20% of the 300 millions of people in the US are under 15 and that 96/1000 [2] receive an antibiotic for pharyngitis.

However an external validation in different resource settings may be warranted before generalization. After validation, this CDR might help physicians to focus RDTs on children at higher risk of GAS pharyngitis and therefore decrease antibiotic prescriptions for children in the low-risk group.

Contributors

Study concept and design; study supervision: FLM, FD, IP, AM.

Acquisition of data: FLM.

Analysis and interpretation of data; critical revision of the manuscript for important intellectual content: FLM, FD, AD, IP, AM.

Drafting of the manuscript: FLM, FD, AM.

Statistical analysis: FLM, FD, AD.

Le Marechal and Dubos (guarantor) have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosures none

Funding none

Competing interest none

Ethics approval No ethical approval was needed for this pooled data meta-analysis

Data sharing statement There is no additional data available

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Fig 1. Expected performance of a clinical decision rules strategy for group A streptococcal pharyngitis in children compared to the rapid diagnostic test strategy.

Fig 2. Identification of clinical decision rules for the diagnosis of group A Streptococcal pharyngitis by a systematic database search.

Fig 3. Post-test probability of the clinical decision rules (CDRs) for the low-risk group of patients compared with the performance of the rapid diagnostic tests on Fagan's nomogram. The pre-test probability considered (prevalence of the disease) was 34%.

Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables

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Funding: none

Conflict of interest: none

ARTICLE SUMMARY

Article focus

- Pharyngitis is a frequent diagnosis in children leading to excessive antibiotic treatments by the inability to distinguish a bacterial and viral cause of the disease despite the availability of rapid diagnostic test, too rarely done in children with pharyngitis.
- Several studies have analyzed the performance of clinical signs and developed clinical decision rules for the diagnosis of group A streptococcal (GAS) pharyngitis in children.
- Through a meta-analysis, this article focus on the methodological quality of these studies and on the value of clinical signs and decision rules that could be helpful to focus rapid diagnostic test to the children with higher risk of GAS pharyngitis.

Key messages

- No symptom considered alone is predictive enough of GAS pharyngitis.
- Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children, but are not performing enough for the positive diagnosis of GAS pharyngitis, which can lead to a still important antibiotic prescription level.
- Therefore, clinical decision rules could be used to focus rapid diagnostic tests to children with high risk of GAS pharyngitis to reduce the use of antibiotic.

Strength and limitations

- Meta-analysis of all relevant articles, from 1975 to 2010 that analyzed the performance of clinical signs and derived or validated clinical decision rules for the diagnosis if GAS pharyngitis in children.
- A decision rule that performed as well as most rapid diagnostic tests to rule out GAS pharyngitis in children was identified, but has not been validated until now.

- Comparison between studies was limited by methodological weaknesses and heterogeneity between patients.

ABSTRACT

Objective: To identify the best clinical decision rules (CDRs) for diagnosing group A streptococcal (GAS) pharyngitis in children. A combination of symptoms could help clinicians to exclude GAS infection in children with pharyngitis.

Design: Systematic review and meta-analysis of original articles involving CDRs in children. The Pubmed, OVID, INIST and Cochrane databases from 1975 to 2010 were screened for articles that derived or validated a CDR on a pediatric population: 171 references were identified.

Setting: Any reference including primary care for children with pharyngitis.

Data extraction: The methodological quality of the articles selected was analyzed according to published quality standards. A meta-analysis was performed to assess the statistical performance of the CDRs and their variables for the diagnosis of GAS pharyngitis.

Primary outcome measure: The main criterion was a false-negative rate in the whole population not any worse than that of a rapid diagnostic test strategy for all patients (high sensitivity, low negative likelihood ratio).

Results Four derived and 12 validated CDRs for this diagnosis in children. These articles involved 10,523 children (mean age, 7 years; mean prevalence of GAS pharyngitis, 34%). No single variable was sufficient for diagnosis. Among the CDRs, that of Joachim et al. had a negative likelihood ratio of 0.3 (95%CI: 0.2-0.5), resulting in a post-test probability of 13%, which leads to 3.6% false-negative rate among low-risk patients and 10.8% overall, equivalent to rapid diagnostic tests in some studies.

Conclusion The rule of Joachim et al. could be useful for clinicians who do not use rapid diagnostic tests and should allow avoiding antibiotic treatment for the 35% of children identified by the rule as not having GAS pharyngitis. Due to its poor specificity, such CDR should be used to focus rapid diagnostic tests to children with high risk of GAS pharyngitis to reduce the antibiotic consumption.

Trial registration: no

Introduction

Acute pharyngitis is one of the most common diseases in the world. It is diagnosed annually in 11 million patients in US emergency departments (ED) and other outpatient settings [1] and is responsible for more than 140 physician office visits and 96 antibiotic prescriptions per 1000 US children under 15 years of age [2]. The group A streptococcal (GAS) form is identified in 20 to 37% of children with pharyngitis [3,4].

The priority over the past 50 years has been the prevention of GAS complications such as local suppurations, invasive infections, and acute rheumatic fever (ARF). These complications are rare in industrialized countries, however; among children treated with antibiotics in GAS pharyngitis, less than 1% have suppurative complications [5], 3/100,000 have invasive infections [6] and 0.08 to 0.15/100,000 ARF [7,8]. ARF rates were declining even before the use of antibiotics because non-rheumatogenic types of streptococci were replacing the rheumatogenic types [9]. The prevention of these complications, however, has induced the large-scale prescription of antibiotics, which in turn might induce drug side-effects and the emergence of multidrug-resistant organisms due to pressure on the ecosystem [10].

National guidelines are different one country to another [11]. To optimize the use of antibiotics, in 2012 the Infectious Diseases Society of America (IDSA) recommended the use of pharyngeal swabs to take samples for bacterial cultures or rapid diagnostic tests (RDT) because the clinical features alone do not reliably discriminate between GAS and viral pharyngitis [12]. These recommendations have changed some medical practices, but adhesion remains partial [13]. Although diagnostic performances of RDT are good (sensitivity [Se], 85-90%, specificity [Sp], 90-100%) [14,15], they are still not widespread used [16], are offered to less than 50% of patients with pharyngitis [17], and antibiotic prescriptions for children with pharyngitis remain excessive in industrialized countries [2]. Moreover, RDT are not

recommended in practice in all settings internationally [18]. Clinical decision rules (CDRs) have been proposed to help physicians decide whether or not the patient needs further tests (RDT or culture) or direct antibiotic treatment without further testing. The IDSA recommends the use of such CDRs [12]. Although several authors have suggested CDRs for children [19-24], most of these have been validated only partially [25-36].

The aim of this study is to conduct the first systematic review, including a meta-analysis, of these CDRs and their variables for the diagnosis of GAS pharyngitis in children, to identify CDRs not any worse than that of a rapid diagnostic test strategy.

Methods

Search strategy and study selection criteria

This systematic search and quality assessment of studies was performed independently by FL and FD in august 2010. To identify eligible original articles, we searched four electronic databases: Medline via PubMed, INIST (Institute for Scientific and Technical Information) at article@inist, database now accessible at www.Refdoc.fr, the OVID library at http://ovidsp.ovid.com/, and the Cochrane library. In the Medline search, we used the medical subject heading terms "pharyngitis" (MeSH, restricted to major topic) and "predictive value of tests" (MeSH), separated by the Boolean operator AND. Limits were set to specify "human" as the species, "all child" as the age, and year of publication from 1975 to 2010, without limits on language of publication. In the other databases only the MeSH term "pharyngitis" was used and less limits to broaden the research: in INIST via Refdoc, we used the terms "pharyngitis" and "children" from 1975 to 2010; in OVID, we used the terms "pharyngitis", "children" and "sensitivity" with limits set to specify "clinical medicine" as journal subset, and year of publication from 1975 to 2010; in the Cochrane library, we used the term "pharyngitis" alone without limits of dates.

The study selection criterion was the presence of original data used to derive or validate a CDR for predicting GAS pharyngitis in a pediatric population. We reviewed the titles of all articles identified by electronic searches and then the abstracts of those that appeared eligible. Related articles and references in the articles that met the selection criterion were examined to identify references that our electronic research might have missed. Eligible articles were fully reviewed.

Quality criteria for the CDR derivation and validation studies

The quality of the selected articles was determined by applying the methodological standards of Wasson et al. [37] and Laupacis et al. [38]. Two of the authors (FL, FD) separately screened each article for the 10 criteria listed below. Each criterion applied to GAS pharyngitis was split into 1 to 4 items (one point per item), as detailed below. Derivation studies could have up to 24 items and validation studies 21. The criteria were:

(i) The outcome for the selected articles was GAS pharyngitis. It should have been defined and diagnosed with the gold standard, a throat culture. The culture technique should have been specified. The test used as the gold standard should have been assessed blinded, without knowledge of the value of the predictive variables. (ii) The predictive values used in the studies that derived each CDR should have been exhaustively identified and well defined, to facilitate its reproducible use. The choice of the variables should have been explained, and the potentially important variables not included should have been mentioned. The studies that validated CDRs should have used the predictive variables as listed and defined in the derivation. Analysis should have been performed blinded to the outcome. (iii) Important patient characteristics should have been described, e.g., age, sex ratio and any characteristics that might cause the predictive value to differ within the cohort of patients, such as the prevalence of GAS pharyngitis. (iv) The study site should have been specified, including the

medical setting and the country. (v) The statistics used to derive the CDRs should have been described and justified. The authors should have assessed the possibility that the logistic regression model overfitted the data [38]. (vi) The statistical performance of the CDRs should have been described. (vii) The reproducibility of the predictive variables and of the CDR should have been assessed. (viii) The study should have been prospective, and the CDR should have been fully validated, in accordance with recommendations [39]: derivation study, internal validation, external validation, and prospective study of the rule's impact on clinical behavior. (ix) The CDR should be clinically sensible, easy to use (simple and quick) and should suggest a course of action rather than a probability of disease. (x) The effects of clinical use should have been prospectively measured. This last criterion (impact of the CDR) was evaluated at point viii.

Main criteria of CDR performance

The aim of a CDR strategy is to identify a group of children at low risk of GAS pharyngitis to allow them to avoid antibiotic treatment for these patients and to propose an action (e.g., RDT) for patients classified in the high-risk group. A strategy including a CDR was considered useful if it did not increase the false negative rate in the overall population (high and low risk patients), compared to a RDT strategy for all patients (Figure 1). The RDT strategy (median Se: 89%, median Sp: 96%) has a median false negative rate of 11% [14]. Therefore, our criteria for evaluating the performance of each CDR were a Se as good as that of RDTs and a probability of GAS pharyngitis in the low-risk group of patients <11%. This corresponds to a negative likelihood ratio (LR–) of 0.2 or less when the prevalence of GAS pharyngitis is 30% [3, 4]. In the literature, a LR– under 0.2 is considered useful [38] and the median LR– for RDTs is 0.15 [14].

Statistical analysis

After the identification of the CDRs, the entire population was described, in percentages and 95% confidence intervals (CI) for dichotomous variables and means and ranges for continuous variables. The absence of the raw data prevented us from calculating the standard deviations. The statistical performance of the variables and the CDRs was analyzed for pediatric studies only and not in studies that included both children and adults. When possible, we focused on children older than 3 years [27], because younger children rarely have GAS pharyngitis [12].

The meta-analysis of the variables included in the CDRs and their validations used the DerSimonian and Laird method [41]. For the Se, Sp, positive and negative predictive values (PPV and NPV), we tested the heterogeneity between studies, applying the likelihood ratio test. For the odds ratio (OR), positive likelihood ratio (LR+) and LR–, we used Cochran's Q test. In analyses with significant heterogeneity or with four or more studies, a random effect model was used to assign the weight of each study. Pooled Se, Sp, PPV, NPV, LR+, LR– and OR with their 95% CIs were calculated for CDRs and their variables.

CDRs in the literature propose different courses of action according to the individual's clinical risk of GAS pharyngitis. In the selected studies, four CDRs proposed a course of action based on three levels of probability of GAS pharyngitis: high risk (antibiotics), intermediate risk (culture and antibiotics if positive), and low risk (no culture, no antibiotics). One CDR proposed a course of action based on two risk groups [20], and two CDRs offered four or five risk groups without any courses of action [19,25]. We chose to identify the CDRs with a useful LR– that would allow us to rule out GAS pharyngitis, as most second-generation RDTs do. Therefore we dichotomized each population into two groups: the low-risk group on one side and the intermediate and high-risk group on the other side (see supplementary material).

Results

Search strategy results

After excluding duplicates, our search strategy identified 65 references from PubMed, another 89 from INIST, 8 from OVID and 9 from the Cochrane database (see flowchart, Figure 2). Reading the titles and abstracts of these 171 references led us to exclude 150 articles that did not meet the inclusion criterion. Complete reading of the remaining 21 articles and reviewing their references, related articles and authors' publications identified 15 additional relevant references. Of these 36 references, 18 were excluded because they did not report the derivation or validation of a CDR on a pediatric population. In the 18 articles that fulfilled the inclusion criterion, six studies derived CDRs [19-24], and 12 validated them in children [25-36]. Of these 18 studies, the article cited as the source from which the World Health Organization's (WHO) CDR [20] was derived did not provide details about it, and the CDR by Centor et al. [19] used for validation in children was derived on adult patients. These two derivation studies were thus screened for methodological quality, but were excluded from the meta-analysis. However, the studies that validated these two CDRs among children [28-31] were included in the meta-analysis.

Patient characteristics

The 16 studies with data for children included 10,523 children. Eleven studies took place in industrialized countries and five in emerging countries. Nine studies were conducted in hospitals or clinics, six in pediatricians' or general practitioners' (GPs) offices, and one in GPs' offices and an ED. Overall, the derivation studies that could be reviewed (n=4) included 963 children (mean number per study: 241, range: 90–356) [21-24]. All the validation studies (n=12) together included 9,560 children (mean number per study: 797, range: 79–1,848) [25-

36]. The mean prevalence of GAS pharyngitis was 34% (median: 34%, range: 24–58%) and did not differ between the derivation and validation studies (33% vs. 34%; p=0.54) or between industrialized and emerging countries (34% vs. 33%; p=0.30). The children's mean age was 7 years, 5.9 in the derivation and 7.2 in the validation sets, 5.7 in the emerging and 8.4 in the industrialized countries. The studies used different inclusion criteria: “pharyngitis” (n=5) [23,24,27,35,36], “suspected GAS pharyngitis” (n=4) [22,26,29,34], “sore throat” (n=3) [28,31,33], “new upper respiratory tract infection” (n=2) [21,25] and both “new upper respiratory tract infection” and “sore throat” (n=2) [30,32].

Methodological quality for derivation and validation studies

Overall, the derivation studies correctly followed a median of 65% of the quality criteria (range: 13-83%). The derivation of WHO’s CDR was not found. The validation studies correctly followed a mean of 69% of these quality criteria (range: 43-86%) (Table 1).

One study used an RDT as the gold standard [24], and two others used RDTs or throat culture [29,34]. No derivation studies defined a predictive variable; three validation studies did so for at least one variable (i.e., cervical lymph node [25,27,30], abnormal pharynx [25], exudate [30]), but 7/12 validation studies changed a variable (e.g., tender node for node, fever≥38°C for fever>38°C). All studies described the CDRs, although one modified it [36]. No study specifically described whether assessments were blinded, but for validation studies, we considered that a prospective study based on the culture result and without any RDT validated this item. One derivation study simplified a rule without reconducting the statistical analyses [24]. Only one study was retrospective [34].

Performance of the variables

The CDRs considered 17 variables in all, most frequently lymph nodes, exudate, age, fever and cough. The supplementary materials include a table describing the types of variables by CDR and the details of the CDRs. Table 2 presents the meta-analysis of the statistical

performance of these variables. “Node >1.5 cm”, “sore throat” and “no diarrhea” each had a LR– under 0.5. The sensitivity of these three variables exceeded 0.81, and their NPV exceeded 0.72. The statistical performance of “Node >1.5 cm” was not reproducible with the other “node” variables. “Scarlatiniform rash” had the highest LR+ (4.7) and OR (4.8). All other LR+ were less than 2.

Performance of the CDRs

After meta-analysis of the validation studies, three rules had high Se (99%, 95% and 88%) and NPVs (87 to 88%). However, the rules of McIsaac et al. and Attia et al. were not discriminative (Sp, 14% and 4%), and were negative for only 10% and 3% of the population respectively (Table 3). These rules were therefore not useful in clinical practice. The rule tested by Joachim et al. had one of the best LR– (Table 3), with a value of 0.3 (95% CI: 0.2-0.5), which should help clinicians to rule out the diagnosis of GAS pharyngitis. Application of this CDR brought the probability of GAS pharyngitis down from 34% to 13% when the score of the CDR is negative (Figure 3). The rule of Joachim et al. also had the best performance, with a Se of 88%, a post-test probability of 13% in 28% of the low-risk patients, and a Sp of 35% (95% CI: 30-40). This rule leads to a 3.6% false-negative rate in this low-risk population and 11.5% overall with an RDT strategy for the intermediate and high-risk patient groups and on the assumption that the RDT sensitivity was 89%.

Discussion

The large number of studies and CDRs proposed for the diagnosis of GAS pharyngitis is evidence of physicians' desire to improve their management of this common disease and to limit antibiotic prescriptions, bacterial resistance and costs. Our study shows how difficult it is to develop and validate an effective and useful CDR. We identified 16 articles that described the derivation or validation of seven CDRs for the diagnosis of GAS pharyngitis in

children. The meta-analysis confirmed, as others recently, [42] that symptoms alone were not sufficient to rule out this diagnosis. Examination of the statistical performance of the variables included in the CDRs showed that none had a significant positive (>5) or negative (<0.2) LR [40]. Two CDRs brought the post-test probability of GAS pharyngitis to around 10% [22,24]. Only the CDR of Joachim et al. was considered useful for clinical use to exclude GAS pharyngitis.

The poor performance of each of these variables requires comment. It might be due to the low specificity of some signs (such as rhinorrhea and cervical nodes), their subjectivity in children (sore throat), or a lack of definition. For these reasons, several variables might have been recorded differently from study to study and possibly within some studies. Because the individual variables predict GAS pharyngitis so poorly, researchers have suggested combining potential predictive variables within a CDR. Our systematic review of standards for the derivation of CDRs [37,38], however, shows that none of the studies followed all of the methodological quality criteria, in particular, the studies that derived CDRs did not. The construction of two CDRs was not available for methodological analysis [20,25,43]. A rule that proposed an empirical simplification of the Breese score, without following any methodological standards was not included [44]. Two other rules not specifically derived for children [19,21], have nonetheless been used for validation in a paediatric population [28,29,32-35], despite the methodological requirement that rules be applied only in populations with the same characteristics as those used in the derivation sets [39]. We also identified statistical biases. When a CDR is derived on a population, the validation set should not include members of the derivation set [21]. Moreover, the logistic regression model of multivariate analyses in some studies might have been overfitted [19,23]. Finally, the validation of a CDR may entail its refinement [24,36], which in turn requires a new validation. The CDRs with the lowest LR– in our meta-analysis were those of Attia et al. [22]

and Joachim et al [24], which brought the post-test probability of GAS pharyngitis down to 9 and 13% respectively. Nonetheless, the CDR by Attia et al. was validated only once [36] and was not discriminative for clinical practice. The rule developed by Joachim et al. performed best but has not been externally validated yet and requires the collection of nine variables for its application, which may limit its use in practice. Since CDRs were more useful than individual symptoms, they might help the clinicians who do not use RDTs in ruling out the diagnosis of GAS pharyngitis. The interquartile range of LR– for second-generation RDTs varies from 0.07 to 0.19 [14]. Thus the probability of GAS pharyngitis would have been reduced from 34% to a post-test probability of less than 10% for most RDTs [14,15]. Compared to this full RDT strategy, the CDR of Joachim et al. leads to a maximum 11.5% false-negative rate globally: 3.6% in the low-risk group of patients (28%) and 7.9% in the intermediate and high risk group (72%), if we assume a RDT strategy with 89% sensitivity (probably an underestimate in this group). Nevertheless, none of the CDRs included in this study reached the level of performance required to bring both the probability of GAS pharyngitis and the risk of a false negative test to less than 10%, as most RDTs do.

Our study has some limitations. Because of the lack of access to individual data, except from two authors who provided the complete set of data from their derivation study [23,24], we could only perform a meta-analysis of the pooled data. Moreover, the populations involved in our analysis were heterogeneous and difficult to compare. These differences concerned (i) the objective of the study, since some studies sought to validate a CDR while others tested RDTs [35] or serologic titers [28]; (ii) the inclusion criteria, which differed between CDRs and even within the same CDR; and (iii) the mean age of the patients, which might influence the prevalence of the disease and the type of symptoms [27]. The prevalence of the disease varied and could double between studies, as a result of differences in patients' ages [31] or study sites or because of a short study period when GAS might be more or less

prevalent [19,22,25]. Although prevalence did not influence sensitivity, specificity or the LRs of the variables, it might influence the choice of variables for building the CDR, especially when methodological standards are not adhered to closely. A spectrum bias is possible if reference standards were not performed in all patients of the included studies. Variables might be defined differently between studies of the same CDR, and one CDR might suggest a different course of action in different studies [36]. Another important variation may come from the definition of the disease (pharyngitis), which was not provided in the studies and which varies between countries [12,45]. We had to create artificial risk groups and courses of action for three CDRs, although they had not been derived for that purpose; our results thus cannot reflect exactly the performance of each risk group. Finally, a review was recently published on this subject but focused the literature research on the signs and symptoms of pharyngitis, when we focused it on CDRs. Findings were slightly different in terms of articles reviewed and not different in terms of performance of individual variables. The CDR by Attia et al. was identified by their systematic research but not the one by Joachim et al [42].

Lastly, we must question whether physicians will use a CDR at all for a well-known and usually banal disease. It might be useful for countries were the RDT use is not recommended in current practice [18]. It might also well interest the 50% of physicians who do not use RDTs at all [13,16,17]. It will do so only, however, if the CDR produces accurate results, is useful, is well validated and is easy to use. The heterogeneity of patients between studies might necessitate a validation and a comparison of available CDRs in a single pediatric population. Our results showed that one CDR has a performance that did not produce a false-negative rate for GAS pharyngitis higher than that of the RDT strategy [20]. The rule has only 35% Sp; but its use could avoid about 6 millions of antibiotic prescriptions in American children (< 15 y.o.) when considering that almost 20% of the 300 millions of people in the US are under 15 and that 96/1000 [2] receive an antibiotic for pharyngitis.

However an external validation in different resource settings may be warranted before generalization. After validation, this CDR might help physicians to focus RDTs on children at higher risk of GAS pharyngitis and therefore decrease antibiotic prescriptions for children in the low-risk group.

Contributors

Study concept and design; study supervision: FLM, FD, IP, AM.

Acquisition of data: FLM.

Analysis and interpretation of data; critical revision of the manuscript for important intellectual content: FLM, FD, AD, IP, AM.

Drafting of the manuscript: FLM, FD, AM.

Statistical analysis: FLM, FD, AD.

Le Marechal and Dubos (guarantor) have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosures none

Funding none

Competing interest none

Ethics approval No ethical approval was needed for this pooled data meta-analysis

Data sharing statement There is no additional data available

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Fig 1. Expected performance of a clinical decision rules strategy for group A streptococcal pharyngitis in children compared to the rapid diagnostic test strategy.

Fig 2. Identification of clinical decision rules for the diagnosis of group A Streptococcal pharyngitis by a systematic database search.

Fig 3. Post-test probability of the clinical decision rules (CDRs) for the low-risk group of patients compared with the performance of the rapid diagnostic tests on Fagan's nomogram. The pre-test probability considered (prevalence of the disease) was 34%.

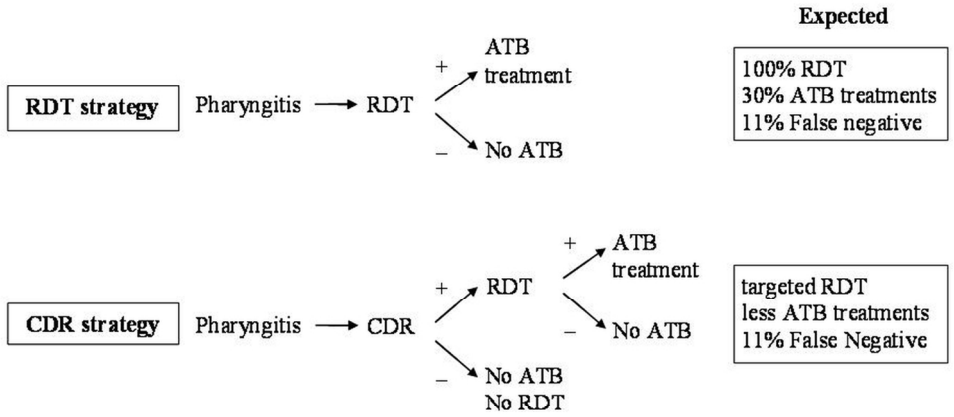
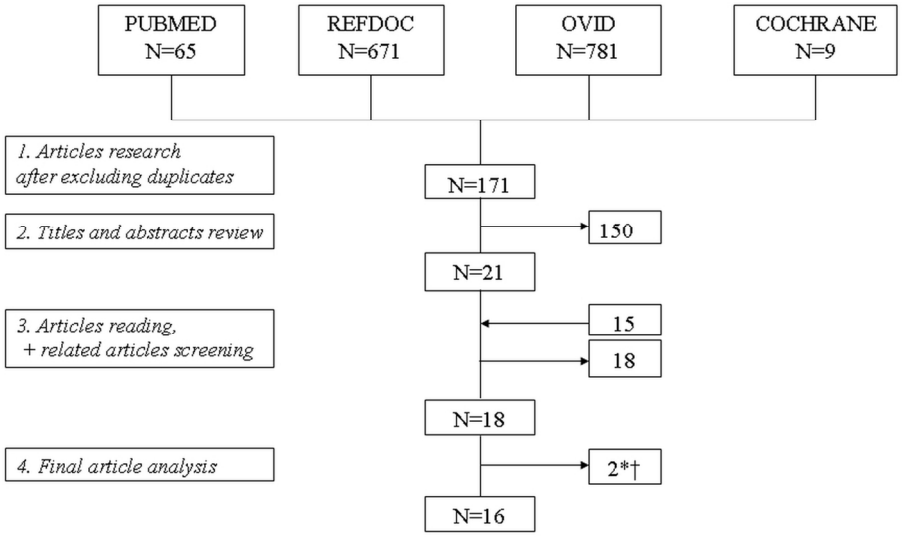


Figure 1.

Figure 1. Expected performance of a clinical decision rules strategy for group A streptococcal pharyngitis in children compared to the rapid diagnostic test strategy

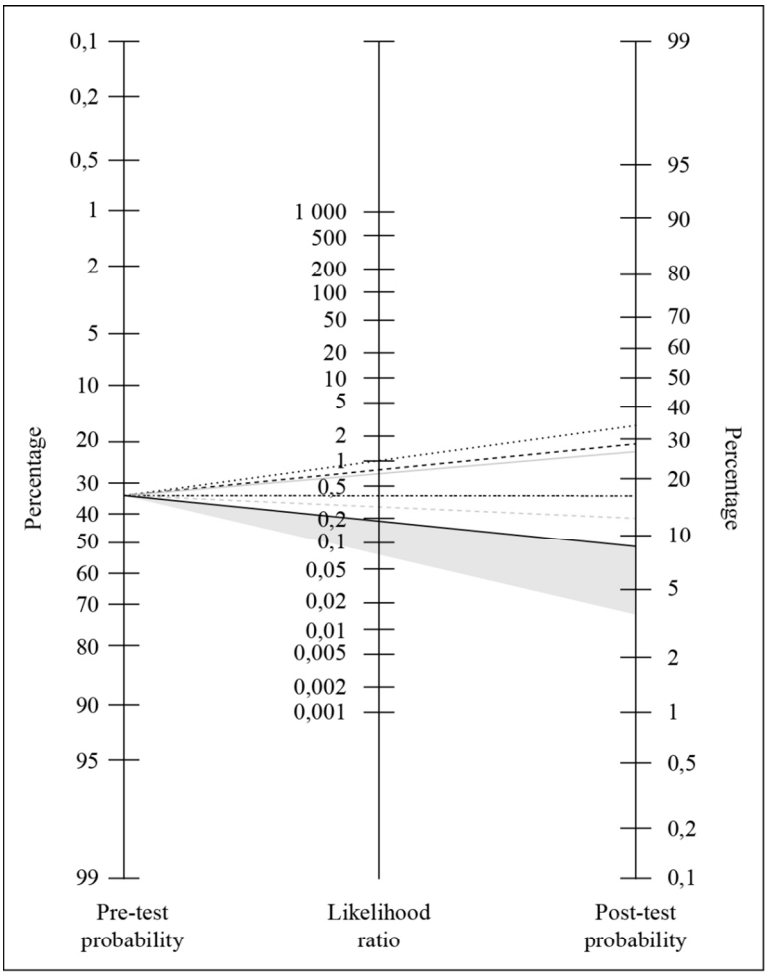
ATB, Antibiotics; CDR, Clinical Decision Rules; RDT, Rapid Diagnostic Test

119x90mm (300 x 300 DPI)



* An excluded CDR, derived in an adult population but validated twice in children, was considered for the methodological quality analysis (19).
† The derivation study of a CDR was not available for analysis [14].

Identification of clinical decision rules for the diagnosis of group A Streptococcal pharyngitis by a systematic database search.
119x281mm (300 x 96 DPI)



··· WHO's CDR (post-test probability of 34%)
-- The CDR of Centor et al. (post-test probability of 29%)
— The CDR of Breese et al. (post-test probability of 27%)
·-·- The CDR of McIsaac et al. and Smeesters et al. (post-test probability of 17%)
-·- The CDR of Joachim et al. (post-test probability of 13%)
— The CDR of Attia et al. (post-test probability of 9%)
◥ 25-75th quartiles for Rapid Diagnostic Tests [13]

Post-test probability of the clinical decision rules (CDRs) for the low-risk group of patients compared with the performance of the rapid diagnostic tests on Fagan's nomogram. The pre-test probability considered (prevalence of the disease) was 34%.
90x136mm (300 x 300 DPI)

Supplementary material

Variables in the Clinical Decision Rules (CDRs) for the Diagnosis of Group A Streptococcal Pharyngitis and Description of these CDRs

Table. Variables of the CDRs Derived for the Diagnosis of Group A Streptococcal Pharyngitis.

Variables	Breese [23]	Centor* [17]	WHO [18]	McIsaac [19]	Attia [20]	Smeesters [21]	Joachim [22]
Cervical lymph nodes	X	X	X	X	X	X	X
Pharyngeal exudate†	X	X	X	X	X		
Age	X			X		X	X
Fever	≥38°C	X#		>38°C		>38.5°C	
Cough	X	X		X		X	
Headache	X					X	X
Sore throat	X						
Sudden onset						X	X
Abdominal pain						X	X
Conjunctivitis						X	X
Diarrhea						X	X
Coryza					X	X	X
Petechia on the palate						X	X
Viral exanthema						X	
Scarlatiniform rash					X		
Month	X						
White blood cell count	X						

*Rule derived in adult patients but validated twice in children
†pharyngeal or tonsillar exudates or swelling
#History of fever

Each CDR is detailed below. The low risk group as determined from identified studies is underlined at the bottom of each CDR.

The CDR derived by Breese et al. [23]

Predictive variable	Points assigned		
Age (years)			
2 or under	1		
3, 15 or more	2		
4, 11 to 14	3		
5 to 10	4		
Months			
July, August, September	1		
June, October, November	2		
January, May, December	3		
February, March, April	4		
Signs and symptoms	**Yes**	**No**	**Unknown**
Fever ≥ 100.5 F	4	2	2
Sore throat	4	2	2
Cough	2	4	4
Headache	4	2	2
Abnormal Pharynx	4	1	3
Abnormal Cervical glands	4	2	3
White blood count			
0-8.4	1		
8.5-10.4	2		
10.5-13.4	3		
13.5-20.4	5		
20.5 or more	6		
Not done	3		

For each patient, they recorded 9 variables, assigned points to each of them, calculated the score and did a throat culture. They created 4 groups: patients with less than 50% risk of GAS pharyngitis were assigned to the groups “no” or “maybe no”; patients with more than 50% were assigned in the groups “yes” or “maybe yes”. A score ≤ 29 defined the low risk group.

The CDR derived by Centor et al. [17]

They derived the CDR on adults. Four of 11 signs and symptoms were statistically correlated with a positive GAS culture: swollen tender anterior cervical node, tonsillar exudates, fever history and lack of cough. Each variable was worth one point. The 5 probability groups had an increasing prevalence of GAS pharyngitis. A score ≤ 2 defined the low risk group.

The CDR derived by the WHO [18]

The WHO recommended in a book that "a child who has tender, enlarged lymph nodes in the front of the neck, and a white exudate on the throat is classified as having streptococcal sore throat". The absence of both clinical signs defined the low risk group.

The CDR derived by McIsaac et al. [19]

The CDR was derived on children and adults. Five of 23 variables were statistically associated with GAS pharyngitis: age, temperature >38°C, no cough, tender anterior cervical adenopathy and swollen tonsils or exudate. Each variable was worth one point. To adjust for age, children aged 3 to 14 years were assigned 1 point, those aged 15 to 44 received a score of 0 and those aged 45 or more received a score of -1. If the total score was :

- 0 or 1: no culture or antibiotic required.
- 2 or 3: culture and antibiotic if positive.
- 4 or 5: culture and antibiotic if positive.

A score ≤ 1 defined the low risk group.

The CDR derived by Attia et al. [20]

Four of the 12 clinical variables screened were statistically associated with GAS pharyngitis: coryza, swollen tonsils, tender enlarged nodes and scarlatiniform rash. Patients were split into 3 probability groups:

- High-risk group: enlarged nodes, swollen tonsils, no coryza with or without scarlatiniform rash (treat, no test).
- Moderate-risk group: absence of one or two signs of the signs above, but no scarlatiniform rash (test).
- Low-risk group: coryza, with no nodes, no swollen tonsils, and no scarlatiniform rash (no treatment, no test).

The absence of nodes, swollen tonsils, and scarlatiniform rash defined the low risk group.

The CDR derived by Smeesters et al. [21]

They used the signs and the symptoms recommended by the IDSA practice guidelines, which included viral signs (conjunctivitis, coryza, cough, diarrhea, viral-like exanthema) and bacterial or GAS signs (fever >38.5°C, tender cervical node, headache, petechiae on the palate, abdominal pain and sudden onset <12 hours). Age, viral and bacterial signs had β values of 2.8, 0.8 and 1.0 respectively:

- Age: ≤35 months (20 pts), 36-59 months (6 pts), ≥60 months (2 points)
- Viral signs: none (0 pt), 1 sign (7 pts), ≥2 signs (10 pts)
- Bacterial signs: none (10 pts), 1 sign (-2 pts), ≥2 signs (-2 pts)

The score was calculated for each patient. If bacteriological diagnosis was unavailable, a patient with a score ≥8 received symptomatic treatment and a patient with a score <8 received antibiotic treatment. If bacteriological diagnosis was available, the patient received:

- score <5: antibiotic,

- score 5-7: antibiotic if positive culture,
- score ≥8: symptomatic treatment.

A score ≥ 8 defined the low risk group.

The CDR derived by Joachim et al. [22]

They simplified the CDR derived by Smeesters et al. to use only 9 variables. Patients received one positive point for each bacterial sign (tender cervical node, headache, petechiae on the palate, abdominal pain and sudden onset <12 hours) and one negative point for each viral sign (conjunctivitis, coryza and diarrhea). They also received points for age (≤35 months: 1 point, 36-59 months: 2 points, ≥60 months: 3 points). If no bacteriologic diagnosis was available, symptomatic treatment was given for a score ≤2 and antibiotics for a score ≥3. If bacteriologic diagnosis was available, the patient received:

- score ≤2: no RDT, symptomatic treatment,
- score=3: RDT and antibiotics if positive,
- score ≥4: no RDT, antibiotics.

A score ≤ 2 defined the low risk group.